The Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: a Systematic Review

Supplementary Appendices

Version: Final

Date: 20 Jan 16
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1. *Systematic review protocol, including example Medline search strategy*
Systematic Review Protocol

1. Title of review:
The safety of oral propranolol in infantile hemangioma: a systematic review

2. Reviewer Contact Details:
See full article

Final version: 10 Feb 2015
Amended version: 03 Sep 2015*

* Amended version incorporated detailed methods regarding adverse event coding, updated product marketing information, and minor administrative changes
3. Background

For background information on infantile hemangioma (IH), please refer to the publication by Léauté-Labrèze et al., 2015:

“Infantile hemangiomas (IH) are the most common soft-tissue tumors of childhood, occurring in 3 to 10% of infants. Lesions are usually not present at birth, but are generally diagnosed during the first 4 to 6 weeks of life, with most growth occurring during the first 5 months. Nearly all IH exhibit characteristic evolution consisting of 3 phases: proliferation, stabilization, and slow spontaneous involution. Whilst most follow an uncomplicated clinical course, about 12% result in complications, which can be life- or function-threatening or lead to ulceration, permanent scarring or disfigurement and require referral to a specialist. Many IH leave permanent sequelae with potential psychological morbidity in affected children and parents.”

Historically, systemic corticosteroids were the mainstay treatment for IH, with interferon alpha and vincristine used in lesions refractory to therapy. The efficacy of these treatments is variable and all have associated safety concerns.

In 2008, cases of IH regression were reported in children treated with oral propranolol, a non-selective beta-adrenergic blocking agent. Numerous retrospective studies and case reports and a few small placebo-controlled trials have subsequently supported the efficacy of this treatment (generally at a dose of 2 mg/kg/day).”

All reported cases used off-label propranolol, either using a marketed propranolol solution for other indications or by the compounding of propranolol tablets. Propranolol is now considered as first-line therapy for IH requiring systemic therapy, despite the initial paucity of adequately conducted controlled clinical trials and previous absence of a pediatric formulation. This has been confirmed by several systematic reviews and meta-analyses focused on the assessing effectiveness of oral propranolol.

A pediatric-specific formulation of propranolol (Hemangiol®/Hemangeol®) has recently been developed for the treatment of IH requiring systemic therapy. It has been through clinical development, including one comparatively large randomized controlled trial, and was recently authorized for use by the EMA, FDA and SwissMedic in 2014 and in Australia in 2015. Hemangiol is the only internationally approved therapy for the treatment of IH requiring systemic therapy.

Propranolol has well characterized pharmacological properties and had been in clinical use largely for cardiac indications since the 1950s. In children, its clinical use is accepted in several situations such as hypertension, arrhythmias, tetralogy of Fallot spells, hypertrophic cardiomyopathy, thyrotoxicosis, phaeochromocytoma, and migraine.

The exact mechanism of action of propranolol in the treatment of proliferating IH is unknown, although several mechanisms are likely to be involved: a local hemodynamic effect, an anti-angiogenic effect, and an apoptosis-triggering effect on capillary endothelial cells.

The overall safety profile of propranolol use in IH, although currently considered acceptable, is less well established than for other indications. Given the recent, rapid adoption of propranolol as first line therapy in this indication; the authorization of the first pediatric...
formulation of propranolol for the treatment of IH; and the subsequent accumulation of published evidence in this field, it is felt that a systematic review of the global safety profile of oral propranolol use in the treatment of IH is essential, especially given the very young age of patients and the potential long-term consequences of treatment.

4. Clarification of research question and scope

4.1 Purpose of the decision to be made
The overall aim of this review is to evaluate the safety profile of oral propranolol in the treatment of IH.

4.2 Clear definition of the intervention
Oral propranolol treatment considered as the intervention will include:

- New pediatric formulation of oral propranolol marketed as Hemangiol®/Hemangeol® (clinical development code V0400SB)
- Off-label oral propranolol solutions
- Off-label propranolol tablets compounded and reformulated as a solution

4.3 Place of the intervention in the treatment pathway(s)
This review will aim to focus on the use of oral propranolol as first-line therapy in the treatment of IH requiring systemic therapy (indication for Hemangiol®/Hemangeol®). However, given that this indication for treatment has only recently been defined, the search and selection criteria will not be limited by this definition. It will be assumed that all IH treated with oral propranolol fall into the category of IH requiring systemic therapy; subgroup analyses may be performed to take into account any previous therapy.

4.4 Relevant comparators
This is a systematic review of oral propranolol only. However, for comparative studies presenting well-defined safety data for pre-specified comparator groups (if present), safety data may be captured for potential comparative analysis.

4.5 Population and relevant sub-groups
Eligible patients are those with IH requiring pharmaceutical treatment. Although the majority of IH growth occurs during the first 5 months (Hemangiol® treatment is to be initiated in infants aged 5 weeks to 5 months), the search and selection criteria will not limit the population age.

Relevant subgroups for possible analysis are as follows:

- Age at initiation of therapy (e.g. ≤5 weeks [corrected age if premature], >5 weeks to 5 months, >5 months)
- Location of IH (e.g. facial, airway, ocular/peri-ocular)
- Type of IH (superficial, deep, segmental, mixed)
- Target dose or dose of propranolol received (e.g. <1, 1, 2, 3, <3 mg/kg/day)
- Duration of propranolol treatment (e.g. <6 months, ≥6 months)
- Period of treatment: up-titration/post up-titration
• Previous therapy (yes [+details]/no)

5. Focused review questions

What is the safety profile of oral propranolol in the treatment of IH requiring systemic therapy?

Specifically:

1. What is the current known profile of adverse events for oral propranolol in IH?
2. What is the occurrence of identified risks with oral propranolol: cardiovascular disorders (hypotension, bradycardia, aggravation of AV conduction), respiratory disorders (bronchospasm and bronchial hyperreactivity) and metabolic and nutritional disorders (hypoglycemia/related seizure); what duration and type of safety monitoring are necessary at treatment initiation (including routine echocardiography or ECG)?
3. What are the rare events and new events, whether expected through use in previous indications or previously unknown events in this new indication?
4. What is the occurrence and nature of events leading to temporary or permanent discontinuation of propranolol?
### 5.1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Inclusion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients diagnosed with infantile hemangioma</td>
<td>There will be no limit placed on the age of patients, as IH generally starts to involute naturally at around 1 year of age. A potential subgroup analysis by age may be performed if data permit to differentiate between proliferative and non-proliferative phases of IH.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Oral propranolol (V0400SB [Hemangiol®/Hemangeol®] or off-label solution/compounded formulation)</td>
<td>V0400SB is the product code for the now marketed Hemangiol®/Hemangeol®. Off-label propranolol use in the form of a solution (marketed or compounded formulation) will be included.</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>NA</td>
<td>No comparators will be specified, but well-defined comparator safety data (if present) may be captured for comparative analyses if appropriate.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Safety, adverse events</td>
<td>All articles reporting either at least one AE, or detailing the assessment of safety in the form of AEs (whether or not an AE occurred) will be included.</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>No minimum duration</td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td>All</td>
<td>Study type will not be limited due to the paucity of RCTs in the field and the benefits of using observational studies for the reporting of safety data. However, case series and case reports of less than 10 patients will not be included.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English</td>
<td>English language limits are imposed due to logistical reasons.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Full papers only</td>
<td>Abstracts, posters, conference reports, and responses to the editor will not be included.</td>
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6. Search Strategy

6.1 Search terms

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<th>Terms</th>
<th>Thesaurus</th>
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<td>Population</td>
<td>Terms for infantile hemangioma/haemangioma</td>
</tr>
<tr>
<td></td>
<td>Excluding brain hemangioma, cavernous hemangioma, hemangiomatosis, liver hemangioma, vertebra hemangioma, PHACES</td>
</tr>
<tr>
<td>Intervention (s)</td>
<td>Terms for newborn, infant, infancy, or child</td>
</tr>
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<td>Safety</td>
<td>Terms for propranolol</td>
</tr>
<tr>
<td></td>
<td>Excluding topical</td>
</tr>
<tr>
<td>Comparators</td>
<td>None</td>
</tr>
<tr>
<td>Outcomes</td>
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</tr>
<tr>
<td>Study design</td>
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</table>

See Appendix 1: Search Strategy for an example Medline strategy.

6.2 Search Limits

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<th>None</th>
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<tr>
<td>Publication types</td>
<td>None</td>
</tr>
<tr>
<td>Date of publication</td>
<td>01 January 2007 to July 2014</td>
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<tr>
<td>Language</td>
<td>English</td>
</tr>
<tr>
<td>Other limits</td>
<td>None</td>
</tr>
</tbody>
</table>

6.3 Sources to be searched

The following electronic databases will be searched in order to find all available published safety data on the use of oral propranolol for the treatment of IH:

- Embase_Embase.com
- Medline_Embase.com

The manufacturer of Hemangiol®/Hemangeol® (Pierre Fabre Dermatologie) holds extensive, currently unpublished safety data on the use of oral propranolol in IH. This review will therefore also incorporate the following Pierre Fabre data: pooled clinical trial data, compassionate use data, pharmacovigilance data and any other unpublished clinical trial data as well as any further key published data identified that has not been captured in the literature search defined in Section 6. Search Strategy.

7. Study Selection

All citations retrieved by the electronic database searches will be screened by 2 reviewers to assess eligibility for inclusion.
8. Data Extraction

Data will be extracted jointly by 2 reviewers, using the same standardized data capture form designed for the capture of AE data from multiple study design types (Appendix 2: Summary of Adverse Events in the Scientific Literature; Jan 2007 to Jul 2014). Data extraction will be checked jointly by the same 2 reviewers. Disagreements will be resolved by discussion.

9. Quality assessment strategy

Risk of bias will not be formally assessed as there is currently no well-adapted, validated checklist for the assessment of the quality of safety reporting of a single intervention across the range of study types expected to be included in this review. A narrative discussion of study quality aspects will be presented.

10. Proposed Data synthesis

All AEs reported in the selected publications will be captured and assigned a SOC and PT by the Pierre Fabre Clinical Department, using the MedDRA dictionary (last version in use), and entered into the data capture form. Due to the expected limited safety information available in the selected publications, severity, seriousness and relationship to treatment will not be assigned. Capture and codage rules are presented in Appendix 3: Rules of Data Capture and Coding.

Due to the expected heterogeneity of study designs and reporting of safety findings for citations retrieved, it is likely that the safety data collected will be summarized descriptively in tables and text, accompanied by a narrative synthesis.

If clinically and statistically appropriate, subgroup analyses will be carried out for characteristics defined in Section 4.5 Population and relevant sub-groups.
Appendix 1: Search Strategy

Example Embase Search Strategy (12 Jan 2015)

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</tr>
<tr>
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<td>'hemangiomatosis'/exp OR 'liver hemangioma'/exp OR 'vertebra</td>
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<td>hemangioma'/exp OR phace NEAR/1 syndrome)</td>
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<td>#20 OR #30</td>
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<td>#25 AND (case NEAR/1 report*:de,ab,ti</td>
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<td>#24 NOT #19</td>
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<td>#8 AND complication*:de,ab,ti</td>
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<td>#19 NOT #20</td>
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<td>noxious) NEAR/2 (effect* OR reaction* OR event* OR outcome*)</td>
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</tr>
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<td>#5 OR #6</td>
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<td></td>
<td>OR 'vertebra hemangioma'/exp)</td>
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</table>
## Appendix 2: Summary of Adverse Events in the Scientific Literature; Jan 2007 to Jul 2014

<table>
<thead>
<tr>
<th>Author Year Country</th>
<th>Type of Study</th>
<th>No. Patients Treated with Propranolol/ No. Completers</th>
<th>Sex ratio F/M</th>
<th>Age at TT Initiation Mean (if not specified) [range]</th>
<th>Type or Localization of IH</th>
<th>Target Dose of Propranolol / planned initiation dose(s) mg/kg/day</th>
<th>Duration of Treatment in completers Mean (range)</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N (%) pts with any AE</th>
<th>AE Notified</th>
<th>AE PT MEDdra term</th>
<th>System Organ Class</th>
<th>N (%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
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</tr>
</tbody>
</table>
Appendix 3: Rules of Data Capture and Coding

1. Rules of capture of AEs
   a. Events captured:
      - Events reported as an AE / adverse drug reaction (ADR) by the authors
      - Vital sign events not reported as AE / ADR by the authors
   b. Terminology chosen: term notified by the author. If several terms (generally two) are notified for a same event, the highest clinical level will be captured, e.g.: choice of “hypotension” if both “blood pressure decreased” and “hypotension” are used.

2. Rules of coding of AEs
   a. Use of MedDRA dictionary, last version in use
   b. Entry of preferred term (PT) and system organ class (SOC) corresponding to the notified event
   c. Process for coding:
      - If the notified term is the same as the low level term (LLT), the PT and SOC are automatically generated
      - If the notified term does not exactly match a LLT, the LLT considered the closest to the notified term on a clinical point of view (e.g.: notified term = gross motor abnormality => LLT chosen = activity motor retarded => PT generated = hypokinesia)

3. Regarding the "study type", the following terminology will be used:
   a. RCT for randomised controlled trial; the comparative product(s) will be specified
   b. OCT for open clinical trial; if any comparator was used, it will be specified
   c. For other studies: it will be specified if the study was retrospective or prospective. As far as possible, these terms will be used if reported by the author(s); if not, they will be deducted from the article and enclosed in "double quotation marks".

4. Regarding the "Type or localization of IH", the following terminology will be used:
   a. The specific localization of IH reported by the author(s)
   or
   b. The generic terminology used by the author(s) (such as problematic, complicated, severe etc.)

If no specific localization or generic terminology is used by the author(s), the term problematic IH will be used and enclosed in "double quotation marks", provided it is specified in the article that IH were at risk of functional impairment and/or cosmetic disfigurement and/or were ulcerated; if not, no generic term will be used. If several localizations are reported in the results of the article, the term Various will be used. It will be specified if patients with PHACES were included or if PHACES was an exclusion criterion.

5. If data are not clearly reported, attempts will be made to contact the author; in the case of no response, we will take the most conservative interpretation of the data (i.e. a worst case scenario will be taken).
References

2. *Synopses of manufacturer clinical study reports*
1. TITLE PAGE

CLINICAL STUDY REPORT

A multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile haemangiomas (IHS) requiring systemic therapy

Investigational product: V0400 (propranolol) 3.75 mg/mL oral solution: 3 mg/kg/day
EudraCT number: 2009-018102-22
Protocol number: V00400 SB 1 02
Phase of development: I
Date of first enrolment: 28 May 2010
Date of last completed: 07 June 2011
Coordinating Investigator: Dr Christine Léauté-Labrèze
Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-Enfants
CHU de Bordeaux
F-33000 BORDEAUX
[tel +33 (0)5 56 79 59 42]
Sponsor Representatives for study report: Head of Therapeutic Area: Alain Delarue, MD, IRPF
[tel +33 (0)5 34 50 61 88]
Pharmacokinetic Study Manager: Laurence Del Frari, IRPF
[tel +33 (0)5 34 50 63 90]
Date of report: 29 May 2012
Study performed in compliance with Good Clinical Practice.

This information may be disclosed in whole or in part, submitted for publication, or form the basis for an industrial property licence only with the written approval of Pierre Fabre Médicament. Pierre Fabre Médicament is the owner of this report.
## 2. SYNOPSIS

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<th>Individual Study Table</th>
<th>(For National Authority Use Only)</th>
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<tr>
<td>Name of finished product:</td>
<td>Referring to Module 5 of the Dossier</td>
<td></td>
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<tr>
<td>Name of active substance (or ingredient):</td>
<td>propranolol hydrochloride</td>
<td>Vol.: ..... Page: .....</td>
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</table>

**Title of study:** A multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile haemangiomas (IHs) requiring systemic therapy

**Coordinating Investigator:** Dr Christine Léauté-Labrèze, Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-Enfants, CHU Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux.

**Investigators:** Physicians (paediatricians or dermatologists) familiar with the management of IH

**Study centres:** Four centres (hospital departments) in France (Bordeaux, Nantes, Lyon, Nice)

**Publication (reference):** Not written to date

**Study period:**
- Date of first enrolment: 28 May 2010
- Date of last completed: 07 June 2011

**Objectives:**
- Primary objective: To characterise the pharmacokinetics (PK) of propranolol (administered as an oral solution [V0400 SB]) at steady-state in infants during a treatment for proliferating IH requiring systemic therapy.
- Secondary objectives:
  - To characterise the PK of a propranolol metabolite (4-OH-propranolol)
  - To assess the efficacy of propranolol on the evolution of the target IH over 12 weeks
  - To document the safety profile of propranolol in the treatment of IH

**Methodology:**
- An open-label, multicentre, repeated-dose study. Infants were stratified to 2 groups according to their age at inclusion, which defined the timing of their PK assessment at steady-state:
  - Group 1: aged from 35 to 90 days inclusive at inclusion; PK assessment after 4 weeks of treatment
  - Group 2: aged from 91 to 150 days inclusive at inclusion; PK assessment after 12 weeks of treatment
- Screening procedures could have been carried out up to 7 days before the baseline visit on Day D0 procedures, or on the same day. Infants received propranolol for the treatment of IH (3 mg/kg/day given twice daily after a 2-week titration period).
- Patients attended for 5 further visits at intervals of 1 to 4 weeks: D7 ± 1 day, D14 ± 1 day, D28 ± 3 days and the end-of-treatment visit at D84 ± 3 days. A phone call was made to the patient’s parent(s) 2 weeks after the end of study treatment at D98 ± 3 days to collect any additional adverse event (AE) data.
- During the 2-week titration period, 2 micro-blood samples were collected at D7 and D14, respectively. Six serial micro-blood samples were collected on one occasion (over a 9-hour period) at steady-state (after 4 weeks or 12 weeks of treatment for the lower and higher age groups, respectively) for propranolol and 4-OH-propranolol assay: T0 (just before morning dosing, 12h after the previous evening administration) and 1h, 2h, 4h, 6h and 9h after the morning administration.

**Number of patients:** Twenty (20) infants were planned to be included in the study (10 infants in each stratification group). Twenty three (23) infants were included (10 in group 1, 13 in group 2).
<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Individual Study Table (For National Authority Use Only)</th>
</tr>
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<tbody>
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<td>Referring to Module 5 of the Dossier</td>
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<tr>
<td>Diagnosis and main criteria for inclusion:</td>
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<tr>
<td>Main inclusion criteria:</td>
<td>Aged 35 to 150 days old, inclusive, at inclusion, Presence of proliferating IH (target haemangioma) requiring systemic therapy: function-threatening IH, IH in certain anatomic locations that often leave permanent scars or deformity, large facial IH, smaller IH in exposed areas, severe ulcerated IH, pedunculated IH,</td>
</tr>
<tr>
<td>Main non-inclusion criteria:</td>
<td>The patient has a medically unstable health status that may have interfered with his/her ability to complete the study (including a life-threatening IH). One or more of the following medical conditions: congenital haemangioma; Kasabach-Merritt syndrome; bronchial asthma; bronchospasm; hypoglycaemia (&lt; 40 mg/dL or at risk); untreated phaeochromocytoma; hypotension (&lt; 50/30 mmHg); second or third degree heart block; cardiogenic shock; metabolic acidosis; bradycardia (&lt; 80 bpm); severe peripheral arterial circulatory disturbances; Raynaud’s phenomenon; sick sinus syndrome; uncontrolled heart failure or Prinzmetal’s angina; documented PHACES syndrome with central nervous system involvement. The Patient was born prematurely and had not yet reached his/her term equivalent age (e.g. an infant born 2 months prematurely could not be included before the age of 2 months). Treatment with proscribed medication (including cardiovascular treatments, anaesthetics and drugs able to induce hypoglycaemia). The Patient had previously been treated for IH, including any surgical and/or medical procedures (e.g. laser therapy).</td>
</tr>
<tr>
<td>Test product, Dose, Mode of administration, Batch numbers:</td>
<td>Test product: V0400 SB (propranolol) oral solution 3.75 mg/mL, in glass bottles 3 mg/kg/day at the end of titration Administration of propranolol oral solution twice daily (morning and late afternoon). The required dose to be administered to the Patient was calculated by the Investigator at each visit and followed by the parent(s) until the next visit. Titration procedure: D0: 1 mg/kg/day D7: increased to 2 mg/kg/day D14: increased to 3 mg/kg/day Propranolol solution 5 mL pipettes graduated in mg of propranolol # SB0753 expiry 02/2011 # 004849 expiry 03/2013 # SB0757 expiry 09/2011</td>
</tr>
<tr>
<td>Other product, Dose, Mode of administration, Batch number:</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Duration of treatment:</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Reference therapy, Dose, Mode of administration, Batch number:</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Name of Company:</td>
<td>Individual Study Table</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
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<tr>
<td>Name of finished product:</td>
<td>Referring to Module 5 of the Dossier</td>
</tr>
<tr>
<td>Name of active substance (or ingredient):</td>
<td>propranolol hydrochloride</td>
</tr>
</tbody>
</table>

**Criteria for evaluation:**

- Pharmacokinetic criteria (primary):
  - Bioanalysis for propranolol and 4-OH-propranolol plasma concentration quantification using a validated LC/MS-MS method.
  - A non-compartmental approach was used to assess PK parameters: Cmax, Tmax, AUClast, AUCl, C1ot/F (only for propranolol) and metabolite/drug ratio for Cmax and AUCl.

- Efficacy criteria (secondary)
  - Investigator on-site qualitative assessments: of change in the IH for paired consecutive patient-visits, of complete/nearly complete resolution of the IH at each scheduled post-baseline visit compared to baseline, and of target IH complications at each scheduled visit;
  - Parent(s)’ on-site qualitative assessment of change in the IH for paired consecutive patient-visits.

- Safety criteria:
  - Adverse events
  - Height, weight, head circumference, temperature, heart rate (HR), systolic/diastolic blood pressure (SBP/DBP), respiratory rate, pulmonary auscultation, liver palpation and global physical examinations (all post-baseline visits)
  - Electrocardiogram (ECG) measurements (D0, D7, D14 and D84): QT corrected for HR according to Bazett (QTcB), Fridericia (QTcF), and Pediatric (QTcP) formulae
  - Laboratory examinations (Baseline and D84)

**Statistical methods:**

- All analyses were descriptive
- Pharmacokinetics:
  - Descriptive statistics on the PK data set (i.e., all patients treated [APT] except patients with major deviations): for both propranolol and 4-OH-propranolol plasma concentrations and PK parameters: arithmetic mean, SD, geometric mean, geometric coefficient of variation (CV), minimum, median, and maximum values were calculated for each age group (for Tmax, only minimum, median, and maximum values were calculated).
- Efficacy and Safety:
  - Descriptive statistics on the APT data set.
  - Adverse events were described by organ system and preferred term of the MedDRA terminology.
  - Vital signs, laboratory assessments, and ECG QTc values and changes were presented over time. Individual values and changes were classified according to normal ranges for vital signs and laboratory assessments and according to CHMP classification for QTc values.
Name of Company: Individual Study Table (For National Authority Use Only)

Name of finished product: Referring to Module 5 of the Dossier

Name of active substance (or ingredient): propranolol hydrochloride Vol.: ......Page: ......

Summary - Conclusions:

Patients’ disposition and data sets
All 23 included patients (10 in group 1, 13 in group 2) were treated and analysed for safety and efficacy (APT data set). Of the 23 APT patients, 1 patient of Group 2 prematurely withdrew at D19 at the Sponsor’s decision following an out-protocol adaptation of dose due to an AE (see §Safety results). Thus, from Visit 5 (D28), efficacy data were available for 22 patients. This patient together with 3 other patients (1 of Group 1 and 2 of Group 2) having had missing PK samples or an out-of-range drug dosing interval were excluded from the PK analysis. Thus 19 patients (9 in group 1 and 10 in group 2) were included in the PK analysis (PK data set).

Pharmacokinetic results

The target dose of 3 mg/kg/day was achieved after a 2-week titration period. Steady-state PK parameters were obtained after repeated twice daily oral administration of propranolol at 3 mg/kg/day in infants for 2 weeks (Group 1) and for 10 weeks (Group 2):

For propranolol: mean Cmax of 78.5 and 79.2 ng/mL were observed in Group 1 and Group 2, respectively, with a corresponding median Tmax of 2 h post-dose in both groups. Mean AUC were 541 and 430 h*ng/mL and oral clearances were 2.71 and 3.27 L/h/kg, in Group 1 and Group 2, respectively. A moderate inter-individual variability in Group 1 (28 to 33%) and a higher inter-individual variability in Group 2 (73 to 103%) were observed for these parameters.

For 4-OH-propranolol: mean Cmax of 6.16 and 3.80 ng/mL were observed with a corresponding median Tmax of 1.09 and 2 h post-dose in Group 1 and Group 2, respectively. Metabolite/parent drug Cmax ratios were 0.0785 and 0.0503 and AUC9h ratios were 0.0593 and 0.0333 in Group 1 and Group 2, respectively. Consequently, exposure to the metabolite accounted for 6% and 3% of total plasma exposure of propranolol over 9 h after administration in Group 1 and in Group 2, respectively.

Pharmacokinetic results are summarised in the table below:

<table>
<thead>
<tr>
<th>Grp</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC (h*ng/mL)</th>
<th>CLtot/F (L/h)</th>
<th>CLtot/F/kg (L/h/kg)</th>
<th>M/P Cmax ratio</th>
<th>M/P AUC9h ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 N</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Geom mean</td>
<td>2.00*</td>
<td>78.5</td>
<td>541</td>
<td>15.2</td>
<td>2.71</td>
<td>0.0785</td>
</tr>
<tr>
<td></td>
<td>Geom CV%</td>
<td>-</td>
<td>32.9</td>
<td>27.5</td>
<td>27.9</td>
<td>27.9</td>
<td>35.9</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1.00</td>
<td>47.8</td>
<td>360</td>
<td>11.4</td>
<td>1.84</td>
<td>0.0524</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>9.00</td>
<td>119</td>
<td>804</td>
<td>22.3</td>
<td>4.05</td>
<td>0.132</td>
</tr>
<tr>
<td>2 N</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Geom mean</td>
<td>2.00*</td>
<td>79.2</td>
<td>430</td>
<td>25.5</td>
<td>3.27</td>
<td>0.0503</td>
</tr>
<tr>
<td></td>
<td>Geom CV%</td>
<td>-</td>
<td>103</td>
<td>73.0</td>
<td>79.1</td>
<td>73.3</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1.00</td>
<td>21.3</td>
<td>116</td>
<td>7.55</td>
<td>1.18</td>
<td>0.00712</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>4.00</td>
<td>448</td>
<td>1193</td>
<td>94.5</td>
<td>12.3</td>
<td>0.202</td>
</tr>
</tbody>
</table>

M/P: Metabolite/Parent drug - not calculated *: median , =12 h
Name of Company: Individual Study Table Referring to Module 5 of the Dossier (For National Authority Use Only)

Name of finished product: Vol.: .......Page: .......

Name of active substance (or ingredient): propranolol hydrochloride

Efficacy results
For on-site assessments by the Investigator, improvement in the IH for paired consecutive visits was reported for the majority of patients at all post-baseline assessments in Groups 1 and 2. The proportion of patients showing improvement peaked at Visit 5 (D28) with 21/23 patients showing improvement compared to the previous visit. All 23 patients showed improvement in the target IH at either Visit 3 (D7) or Visit 4 (D14) and 11 patients showed improvement at all 5 paired assessments. None of the target IH were assessed as having worsened since the previous visit at any post-baseline assessment.

At Visit 7 (D84), complete/nearly complete resolution of the IH was seen in 8 (4 in each group) of the 22 patients.

At baseline there were no major IH complications and no cardiac complications. All complications disappeared over time, confirming the regression of the IH. By Visit 5 (D28) all complications had disappeared except for a single patient in Group 1 with grade 1 ulceration. All patients were clear of complications by Visit 6 (D56).

Assessments by the parents were consistent with those made by the investigators.

Safety results
No deaths occurred during the study. One patient in Group 2 experienced 3 non-drug-related SAEs (hospitalization for mild pallor and crying on one occasion and for moderate acute otitis media on the second occasion). No AEs led to definitive study treatment discontinuation; however, one patient in Group 2 was prematurely withdrawn at the Sponsor’s decision following an out-protocol treatment adaptation due to a drug-related AE: a prolonged QTcB at 4 h post-dose (1 mg/kg) on D14: 467 ms; not associated with prolonged QTcF and QTcP and returning to normality 1 h later (427 ms).

Overall, a total of 75 treatment-emergent AEs (TEAEs) were reported for 20/23 patients. Most TEAEs were reported for similar proportions of patients in both groups. The most common TEAEs (reported for ≥ 3 patients overall), were diarrhoea, nightmare, pyrexia, nasopharyngitis, peripheral coldness, conjunctivitis, cough, bronchitis and toothache. The majority of TEAEs were rated as mild. Two severe TEAEs were reported (pyrexia and blood alkaline phosphatase increased). Related TEAEs (relationship to study drug other than ‘not suspected’) were reported for 7 patients in Group 1 and 8 patients in Group 2. Nightmare (5/23 patients), peripheral coldness (4/23 patients) and diarrhoea (2/23 patients) were the most commonly reported related TEAEs.

Three abnormal laboratory values were assessed as clinically significant by the Investigator for 3 patients. One patient had elevated alkaline phosphatases (ALP) at the final study visit which had returned to normal range at 1-month post-study follow-up. There were also individual occurrences of low MCV for 1 patient and elevated potassium for 1 patient at the final study visit; no repeat test data were reported for these 2 patients. The relationship with the study drug was not excluded for the elevated ALP and potassium.

There were small decreases in supine SBP, DBP, HR and respiratory rate measurements compared to baseline within 4 h of the first dose of propranolol at each up-titration visit. These changes are consistent with the mode of action of propranolol and in general were maintained at subsequent visits. There were small increases in the numbers of patients with low SBP, DBP or HR (according to reference ranges) at some post-baseline assessments with no consistent trend. There were no clinically significant changes in vital signs measurements during the study.

There were no clinically relevant changes in mean body temperature or physical findings over time during the study.

For QTcP, all patients for whom data were available remained ≤450 ms throughout the study and the majority of patients (81.8% to 95.5%) at all time-points had changes in QTcP that were ≤30 ms. Only one clinically significant QTc (QTcB) was reported during the study (prematurely withdrawn patient; above-described).

Conclusion
Once corrected by the body weight, primary PK parameters for propranolol determined in infants are similar to those reported in the literature for adults.

Treatment with propranolol for 12 weeks of proliferating IH in infants resulted in a rapid improvement (within 7-14 days) in all patients. Resolution of the target IH was seen as early as D28 and by D84, 36.4% (8/22) patients had resolution of their target IH. In addition, complications of IH disappeared over time, confirming the regression of the IH.

Propranolol was well tolerated in the overall study population.

Date of report: 29 May 2012
Pierre Fabre Dermatologie
Represented by: Institut de Recherche Pierre Fabre (IRPF)
45, Place Abel Gance
F-92100 Boulogne

1. TITLE PAGE

CLINICAL STUDY REPORT

Full report up to Week 96

A randomized, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind)

Investigational Product: V0400SB
EudraCT Number: 2009-013262-84
Protocol Number: V00400 SB 2 01
Phase of Development: II/III
Date of First Enrolment: February 24, 2010
Date of Last Completed: November 5, 2013
Coordinating Investigator: Christine Léauté-Labrèze, MD
CHU de Bordeaux Hospital, F-33000 BORDEAUX
Phone: +33 (0)5 56 79 59 42
Sponsor Representative for Study Report: Head of Clinical Development: François Brackman, MD, IRPF
3 avenue Hubert Curien, F-31100 TOULOUSE
Phone: +33 (0)5 34 50 63 28

Date of Report: May 5, 2014

Study performed in compliance with Good Clinical Practice.

This information may be disclosed in whole or in part, submitted for publication, or form the basis for an industrial property license only with the written approval of Pierre Fabre Dermatologie.
Pierre Fabre Dermatologie is the owner of this report.
## 2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor: Pierre Fabre Dermatologie</th>
<th>Individual Study Table Referring to Module 5 of the Dossier</th>
<th>(For National Authority Use Only)</th>
</tr>
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<tbody>
<tr>
<td>Name of finished product:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of active substance:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title of study:</td>
<td>A randomized, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind).</td>
<td></td>
</tr>
<tr>
<td>Coordinating Investigator:</td>
<td>Docteur Christine Léauté-Labrèze, MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHU de Bordeaux Hospital, F-33000 BORDEAUX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phone: +33 (0)5 56 79 59 42</td>
<td></td>
</tr>
<tr>
<td>Investigators:</td>
<td>Physicians (mainly pediatricians, dermatologists or surgeons) familiar with the management of IH</td>
<td></td>
</tr>
<tr>
<td>Study centers:</td>
<td>56 recruiting centers in 16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russian Federation, Spain and the USA)</td>
<td></td>
</tr>
<tr>
<td>Studied period:</td>
<td>24 weeks of treatment and follow-up (long term follow-up without study treatment until Week[W]96):</td>
<td></td>
</tr>
<tr>
<td>Date of first enrolment</td>
<td>February 24, 2010</td>
<td>Phase of development: II/III</td>
</tr>
<tr>
<td>Date of last completed</td>
<td>May 8, 2012 (W24 visit)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>November 5, 2013 (W96 visit)</td>
<td></td>
</tr>
<tr>
<td>Objectives:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary:</td>
<td>To identify the appropriate dose and duration of propranolol treatment (as coded V0400SB), out of four regimens of oral propranolol (1 or 3 mg/kg/day twice a day for 3 or 6 months), and to demonstrate its superiority over placebo based on the complete/nearl y complete resolution of the target IH at W24.</td>
<td></td>
</tr>
<tr>
<td>Secondary:</td>
<td>To document the safety profile of the four regimens of propranolol in the treatment of IH in infants aged 35 to 150 days at inclusion.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the long-term post-treatment efficacy and safety of the 4 previous regimens of oral propranolol (over a follow-up period of 72 weeks, up to W96).</td>
<td></td>
</tr>
<tr>
<td>Methodology:</td>
<td>A multidose 2-stage adaptive (seamless phase II/III) design with treatment regimen selection at the end of the first stage, using the methodology described in Posch et al 2005*.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Stage 1:</strong> Five treatment arms (placebo and 4 regimens of propranolol: 1 mg/kg/day 3 months then placebo 3 months, 1 mg/kg/day 6 months, 3 mg/kg/day 3 months then placebo 3 months, 3 mg/kg/day 6 months).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stratified block randomization† (2 strata [age and IH localisation] with 2 levels each) in a 2:2:2:2:1 ratio (propranolol regimens:placebo).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interim analysis of Stage 1 data was performed by an independent statistician.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review of unblinded results by an Independent Data Monitoring Committee (IDMC) consisting of three members (a pediatric dermatologist specialising in IH, a pediatric cardiologist and a statistician specialising in adaptive designs, different to the Independent Statistician preparing the data for review).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The IDMC could choose to either stop the study for safety or futility, or continue with the placebo arm and one or two 'best’ regimens of propranolol (defined as the most efficacious of all regimens with a good safety profile). Furthermore, the IDMC could recommend increasing the sample size at the interim analysis if there was less than 80% conditional power (CP) to demonstrate superiority of the selected regimen over placebo.</td>
<td></td>
</tr>
</tbody>
</table>

†Stratified randomization was performed via an interactive voice response system (IVRS)
<table>
<thead>
<tr>
<th>Methodology (continued):</th>
<th>Stage 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two (or three) treatment arms (placebo and 1 (2) regimen(s) of propranolol).</td>
</tr>
<tr>
<td></td>
<td>Stratified block randomization(^\ast) (same stratified blocks as Stage 1) in a (2):2:1 ratio between the chosen regimen(s) and placebo.</td>
</tr>
<tr>
<td>Primary/W24 database soft lock and analysis were conducted when all of the patients in the study had completed their W24 visit or been prematurely withdrawn from study therapy,</td>
<td></td>
</tr>
<tr>
<td>After W24 database soft lock, the treatments were unblinded to an exclusive list of study personnel,</td>
<td></td>
</tr>
<tr>
<td>the Independent Statistician and the IDMC members. The blind was maintained for the monitoring teams and all investigational site staff until the end of the trial (except the International Coordinating Investigator, reviewer and signatory of the W24 report of December 20, 2012, previously submitted).</td>
<td></td>
</tr>
<tr>
<td>The patient’s complete participation:</td>
<td></td>
</tr>
<tr>
<td>- During the study treatment period (D0-W24): comprised 11 scheduled visits: a screening visit, and 10 visits, starting on baseline visit (Day [D]0, 0 to 14 days after the screening visit, then D7, D14, D21, Week [W]5, W8, W12, W16, W20 and W24 (end of study treatment: EOT);</td>
<td></td>
</tr>
<tr>
<td>- During the post-treatment follow-up period (W24-W96): comprised 4 additional visits, on W36, W48, W72 and W96 (end of study: EOS), for all patients having completed the W0-W24 period.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Planned randomized: approximately 450 patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>180 patients (Placebo: 20/ each active arm: 40)</td>
</tr>
<tr>
<td>Stage 2 + overrun*</td>
<td>270 patients (Placebo: 30, 1-2 selected active arm[s]: 60, unselected active arms [referred to as the &quot;overrun&quot;]: 40 to 60)</td>
</tr>
<tr>
<td>Actually randomized: 460 patients:</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>190 patients: (Placebo: 25, active arms: 40 to 43)</td>
</tr>
<tr>
<td>Stage 2 + overrun*</td>
<td>270 patients (Placebo: 30, selected active arm: 59, unselected active arms [overrun]: 58 to 62)</td>
</tr>
</tbody>
</table>

* Overrun= patients of Stage 2 randomized in the unselected propranolol regimen arms.

<table>
<thead>
<tr>
<th>Diagnosis and main criteria for inclusion:</th>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A patient was eligible if he/she met all of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>- Written informed consent(s) for study participation and the use of the patient’s images obtained according to national regulations from the patient’s parent(s) or guardian(s) prior to performing any study procedures</td>
</tr>
<tr>
<td></td>
<td>- Patient was 35 to 150 days old, inclusive, at inclusion</td>
</tr>
<tr>
<td></td>
<td>- A proliferating IH (target hemangioma) requiring systemic therapy was present anywhere on the body except on the diaper area, with largest diameter of at least 1.5 cm</td>
</tr>
<tr>
<td></td>
<td>- If required by national regulations, registered with a social security or health insurance system and/or whose parent(s) or legal guardian(s) was (were) registered with a social security or health insurance system</td>
</tr>
</tbody>
</table>

\(^\ast\)Stratified randomization was performed via an interactive voice response system (IVRS)
**Diagnosis and main criteria for inclusion:**

- The Patient was ineligible if he/she met any of the following criteria:
  - Had a medically unstable health status that may interfere with his/her ability to complete the study
  - Presented with one or more of the following medical conditions:
    - congenital hemangioma;
    - Kasabach-Merritt syndrome;
    - bronchial asthma;
    - bronchospasm;
    - hypoglycemia (< 40 mg/dl or at risk);
    - untreated phaeochromocytoma;
    - hypotension (< 50/30 mmHg);
    - second or third degree heart block;
    - cardiogenic shock;
    - metabolic acidosis;
    - bradycardia (< 80 bpm);
    - severe peripheral arterial circulatory disturbances;
    - Raynaud’s phenomenon;
    - sick sinus syndrome;
    - uncontrolled heart failure or Prinzmetal’s angina;
    - documented PHACES syndrome with central nervous system involvement
- The Patient (and/or the Mother if she was breastfeeding the patient) had received at least one of the following prohibited medications within 14 days of randomization:
  - Anaesthetic agents, lidocaïne (the exclusion period was shortened to 48 hours, if anaesthesia had been performed for diagnosis investigation e.g. MRI…)
  - Cardiovascular treatments: anti-arrhythmics, calcium channel blockers, ACE inhibitors, inotropic agents, vasodilators (hydralazine hydrochloride…), clonidine…
  - Hypoglycaemic agents or drugs able to induce hypoglycaemia
  - Inducers of hepatic drug metabolism or substrates or inhibitors of CYP2D6, CYP1A2, CYP2C19
  - Anti-ulcer drugs (cimetidine, ranitidine, proton pump inhibitors other than omeprazole and lanzoprazole)
  - Metoclopramide
  - Non-steroid anti-inflammatory drugs (NSAIDs) at anti-inflammatory dose
  - Sympathomimetic agents and parenteral adrenaline
  - Benzodiazepines
  - Neuroleptic drugs (chlorpromazine, sulthopride hydrochloride…)
  - Other drugs: triptans, ergotamine, theophylline, warfarin, thyroxine, floctafenine
### Diagnosis and main criteria for inclusion (continued):

- Had previously been administered at least one of the following prohibited medications: systemic (oral, intra-venous or intra-muscular), intra-lesional or topical corticosteroids, imiquimod, vincristine, alfa-interferon, propranolol or other beta-blockers
- Had previously been treated for IH, including any surgical and/or medical procedures (e.g. laser therapy)
- Patient in whom a systemic corticosteroid therapy was the most advisable in the opinion of the investigator (for Czech Republic)
- The Patient’s mother had been breastfeeding the patient while she was also being treated with beta-blockers (including propranolol) or, she had been breastfeeding the patient within 14 days of randomization while she was also being treated with systemic (oral, intra-venous or intra-muscular) corticosteroids, vincristine or alfa-interferon
- Was known to have a hypersensitivity to propranolol and/or any other beta-blockers
- Had previously experienced an anaphylactic reaction
- One or more of the following types of IH were present:
  - Life-threatening IH
  - Function-threatening IH (e.g. those causing impairment of vision, respiratory compromise caused by airway lesions, etc.)
  - Ulcerated IH (whatever the localisation) with pain and lack of response to simple wound care measures
- Diagnosis of the soft tissue tumour as IH is not clinically certain, particularly in the case of sub-dermal lesions
- Was born prematurely and had not yet reached his/her term equivalent age (e.g. an infant born 2 months prematurely cannot be included before the age of 2 months)
- Had LVEF ≤ 40% and/or cardiomyopathy and/or hereditary arrhythmia disorder
- Was participating in another clinical study or the patient lived in the same household as an infant already participating in this study
- Parent(s) or guardian(s) could not be contacted by telephone in case of emergency.

### Test product, Dose, Mode of administration

**Test product:** propranolol oral solution: 1.25, 2.50 or 3.75 mg/ml.  
**Dose:** 1 or 3 mg/kg/day  
**Mode of administration:** Administration of propranolol oral solution twice daily (0.4 ml/kg; morning and late afternoon around meal intake) for 3 or 6 months.  
**Titration procedure:**
- D0 1 mg/kg/day
- D7 increase to 2 mg/kg/day (for the 3 mg/kg/day arms)
- D14 increase to 3 mg/kg/day (for the 3 mg/kg/day arms)

Dummy titration was used for patients assigned to both of the 1 mg/kg/day dose regimens of propranolol to maintain double-blind conditions. Propranolol was administered for 3 months or 6 months, depending on the assigned regimen. For the two 3 months regimens, placebo was administered for the last 3 months of treatment to maintain double-blind conditions.
**Name of Sponsor:** Pierre Fabre Dermatologie  
**Name of finished product:**  
**Name of active substance:**

**Batches:** Twenty (20) batches of propranolol, and 8 batches of pipettes graduated in ml of oral solution (4 batches of 2 ml pipettes and 4 batches of 5 ml pipettes) were used in the study:

<table>
<thead>
<tr>
<th>Batch number</th>
<th>2 ml pipettes</th>
<th>5 ml pipettes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>propranolol</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1.25 mg/ml:  # SB0853, exp 08/2013  
  # SB0827, exp 05/2013  
  # SB0811, exp 02/2013  
  # SB0798, exp 07/2012  
  # SB0772, exp 03/2012  
  # SB0745, exp 05/2011  
  # SB0755, exp 09/2011 | # 008086, exp 17/05/2014  
  # 006816, exp 10/01/2014  
  # 003346, exp 09/11/2012  
  # 002401, exp 28/04/2012 | # 008088, exp 17/05/2014  
  # 006819, exp 10/01/2014  
  # 002433, exp 28/04/2012  
  # 003350, exp 11/2012 |
| 2.5 mg/ml:  # SB0854, exp 08/2013  
  # SB0828, exp 05/2013  
  # SB0812, exp 02/2013  
  # SB0799, exp 07/2012  
  # SB0746, exp 05/2011  
  # SB0756, exp 09/2011 | # SB0852, exp 08/2013  
  # SB0826, exp 05/2013  
  # SB0813, exp 08/2012  
  # SB0800, exp 04/2012  
  # SB0773, exp 12/2011  
  # SB0747, exp 05/2011  
  # SB0757, exp 09/2011 | # SB0854, exp 08/2013  
  # SB0828, exp 05/2013  
  # SB0813, exp 08/2012  
  # SB0800, exp 04/2012  
  # SB0773, exp 12/2011  
  # SB0747, exp 05/2011  
  # SB0757, exp 09/2011 |
| 3.75 mg/ml:  # SB0855, exp 08/2013  
  # SB0829, exp 05/2013  
  # SB0813, exp 08/2012  
  # SB0800, exp 04/2012  
  # SB0773, exp 12/2011  
  # SB0747, exp 05/2011  
  # SB0757, exp 09/2011 | # SB0855, exp 08/2013  
  # SB0829, exp 05/2013  
  # SB0813, exp 08/2012  
  # SB0800, exp 04/2012  
  # SB0773, exp 12/2011  
  # SB0747, exp 05/2011  
  # SB0757, exp 09/2011 | # SB0855, exp 08/2013  
  # SB0829, exp 05/2013  
  # SB0813, exp 08/2012  
  # SB0800, exp 04/2012  
  # SB0773, exp 12/2011  
  # SB0747, exp 05/2011  
  # SB0757, exp 09/2011 |

**Other product, Dose, Mode of administration, Batch number:** Not applicable.

**Reference therapy, Dose, Mode of administration, Batch number:**

**Reference product:** Placebo  
**Dose:** N/A  
**Mode of administration:** Administration of placebo oral solution twice daily (0.4 ml/kg; morning and late afternoon around meal intake) for 6 months. The same procedures were followed as those described above for the propranolol treatment arms to maintain double-blind conditions.

**Batches:** 7 batches of placebo and 8 batches of pipettes graduated in ml of oral solution (4 batches of 2 ml pipettes and 4 batches of 5 ml pipettes) were used in the study:

<table>
<thead>
<tr>
<th>Batch number</th>
<th>2 ml pipettes</th>
<th>5 ml pipettes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>placebo</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| # SB0852, exp 08/2013  
  # SB0826, exp 05/2013  
  # SB0810, exp 02/2013  
  # SB0797, exp 07/2012  
  # SB0771, exp 03/2012  
  # SB0744, exp 05/2011  
  # SB0754, exp 09/2011 | # 008086, exp 17/05/2014  
  # 006816, exp 10/01/2014  
  # 003346, exp 09/11/2012  
  # 002401, exp 28/04/2012 | # 008088, exp 17/05/2014  
  # 006819, exp 10/01/2014  
  # 002433, exp 28/04/2012  
  # 003350, exp 11/2012 |
| **placebo** |               |               |
| # SB0852, exp 08/2013  
  # SB0826, exp 05/2013  
  # SB0810, exp 02/2013  
  # SB0797, exp 07/2012  
  # SB0771, exp 03/2012  
  # SB0744, exp 05/2011  
  # SB0754, exp 09/2011 | # 008086, exp 17/05/2014  
  # 006816, exp 10/01/2014  
  # 003346, exp 09/11/2012  
  # 002401, exp 28/04/2012 | # 008088, exp 17/05/2014  
  # 006819, exp 10/01/2014  
  # 002433, exp 28/04/2012  
  # 003350, exp 11/2012 |

**Duration of treatment:** 12 weeks (“3 months” regimens) of propranolol followed by 12 weeks of placebo or 24 weeks (“6 months” regimens) of propranolol or placebo.
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Name of finished product: Referring to Module 5 of the Dossier

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Criteria for evaluation:

Efficacy:

Primary efficacy endpoint (W24 analysis):
Evolution of target IH from baseline to W24 evaluated based on the intra-patient blinded centralized independent qualitative assessments (Type I) of W24 photographs of the target IH compared to baseline. A treatment success was defined as a centralized assessment of complete/nearly complete resolution of the target IH at W24 compared to baseline, where nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks.

Secondary efficacy endpoints (W24 and W96 analyses):
- Centralized assessments of the target IH:
  1. Endpoints based on the independent blinded assessments of complete/nearly complete resolution (Type I):
     - Success/failure at W12, W36, W48, W72, and W96 compared to baseline, where treatment success was defined as for the primary efficacy endpoint
     - Time to first sustained complete/nearly complete resolution up to W24 and up to W96
     - Time to first failure up to W96
     - Time to first failure from W24 up to W96
  2. Endpoints based on the independent blinded 3-point scale assessments of IH evolution (Type 2: improvement, stabilization or worsening):
     - Categorical endpoints for target IH evolution between paired patient-visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively). A global improvement was also computed on the W5-W24 period (Yes/No).
     - Time to first sustained improvement (first improvement after which there is no worsening) up to W24
  3. Endpoints based on centralized quantitative assessments:
     - Continuous and categorical endpoints (change in size and colour of target IH) at W12 and W24 compared to baseline

- Investigator’s on-site qualitative assessments at each scheduled post-baseline visit compared to baseline:
  - Categorical endpoints for complete/nearly complete resolution of target IH where “nearly complete” resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks and/or a minimal palpable component,
  - Categorical endpoints for complete resolution (3-point scale: no sequelae; minimal sequelae defined as minimal telangiectasis, macular discolouration and/or textural change; marked sequelae defined as marked textural change with or without distortion of anatomical landmarks or skin contours). Success/failure at W48 based on this assessment (where a success corresponds to a complete resolution of the target IH without sequelae or with minimal sequelae) was defined as the key secondary efficacy endpoint,
  - Time to first sustained complete/nearly complete resolution up to W24 and up to W96,
  - Time to first sustained complete resolution without sequelae or with minimal sequelae up to W24 and up to W96
  - Time to first failure up to W96
- Investigator’s on-site qualitative assessments of paired consecutive patient-visits (each scheduled post-baseline visit compared to the previous scheduled visit):
  - Categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening)
  - Time to first sustained improvement (first improvement after which there is no worsening) up to W24 and up to W96
  - Time to first worsening up to W96
Name of Sponsor: Pierre Fabre Dermatologie

Name of finished product: Referring to Module 5 of the Dossier

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Criteria for evaluation:

**Efficacy (continued):**

- Parent(s) or guardian(s)' on-site qualitative assessments at each scheduled post-baseline visit compared to the previous scheduled visit:
  - Categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening)
  - Time to first sustained improvement (first improvement after which there is no worsening) up to W24 and up to W96
- Other investigator on-site qualitative assessments at each scheduled post-baseline visit:
  - Categorical endpoints based on assessments of target IH complications: functional impairment/ulceration/haemorrhaging
  - Categorical endpoints based on qualitative assessments of complete resolution of non-target facial IH and non-facial IH at each scheduled post-baseline visit (3-point scale: no sequelae; minimal sequelae; marked sequelae)
  - Categorical endpoints based on whether or not invasive procedures were carried out during the study on the target/non-target facial/non-facial IH.
- Other efficacy endpoints:
  - Intake of IH treatment (systemic or local beta-blockers, systemic or local corticoids and laser) during the follow-up period

**Safety:**

Adverse events: continuous assessment

Vital signs (height, weight, head circumference, temperature, heart rate, blood pressure, respiratory rate), pulmonary auscultation, liver palpation and global physical examinations (each scheduled visit + T1h-2h and 4h on D0, D7 and D14 for cardio-vascular vital signs)

ECG measurements (each scheduled visit except W5, W8, W16 and W20)

Laboratory examinations (Screening, W12 and W24/EOT)

Neurodevelopment assessments (Screening, W24/EOT, W96/EOS)

2-dimensional cardiac ultrasounds (Screening, W96/EOS)

Note that ECGs during the study treatment period (including the ECG at the W24 visit), were assessed by an independent physician in order to avoid the risk of treatment unblinding. ECG measurements assessed during the study treatment period (including the ECG at the W24 visit) were not provided to the site study teams. Following each ECG assessment from D0 to W12, the independent physician advised the investigator whether or not, it was safe to continue study therapy.

**Statistical methods:**

All critical efficacy tests were one-sided with a nominal level of $\alpha=0.005$

The level of two-sided tests used for safety is otherwise 0.05

**Interim analysis and IDMC’s recommendation:**

The interim analysis was conducted by the Independent Statistician and reviewed by the IDMC after the first 188 patients treated had completed their visit W24 or been prematurely withdrawn from the study therapy.

The recommendation of the IDMC was to continue the study with one single active dose (3 mg/kg/day for 6 months): this information was kept blinded to the whole study team except the IDMC members, the Independent Statistician and the IVRS team) and placebo, without sample size adjustment/re-estimation.

In the meantime, accrual in the study had continued and the planned sample size had been reached with 460 patients randomized in the trial on November 24, 2011 before the IDMC recommendations were made.
Data sets

The data sets on which the efficacy analyses were performed are the following:
- Intention-to-treat (ITT) data set: all randomized patients in Stage 1 and all the patients in Stage 2 randomized to placebo or the selected regimen of propranolol and having received at least one dose of study therapy (or in the case of uncertainty).
- Per-protocol (PP) data set: a subset of the ITT data set composed of patients without any major protocol deviations, except major deviation for prohibited treatments (after randomization and before the W24 evaluation) that may be used to treat IH.
- ITT with overrun data set: all randomized patients in Stage 1 and all randomized patients in Stage 2 (including the overrun patients=Stage 2 patients on non-selected regimens) who have received at least one dose of study therapy (or in the case of uncertainty).
- Safety data set: all randomized patients having received at least one dose of study therapy (or in the case of uncertainty) during the first or second stage.

Efficacy analyses

Primary analysis of the primary endpoint (W24 analysis)

The primary analysis of the primary endpoint compared in the ITT data set the success rate (complete/nearly complete resolution at W24) rate(s) on the selected regimen(s) of propranolol to placebo.

The objective was to test the superiority of the selected regimen using the methodology described in Posch et al 2005, for an adaptive confirmatory design with dose selection at an interim analysis. The methodology incorporates two key principles: application of the closed testing procedure and combination tests for all intersection hypotheses by using Simes’ adjustment.

This methodology guaranteed that the familywise type I error rate was maintained at the nominal level of 0.005.

The primary efficacy analysis data set (ITT data set) consisted of all the patients randomized in Stage 1 and of the patients randomized in Stage 2 to either placebo or the selected regimen of propranolol and having received at least one dose of study therapy (or not in case of uncertainty).

Sensitivity and adjusted analyses of the primary endpoint (W24 analysis)
- A sensitivity analysis of the primary endpoint was carried out on the PP data set, based on the same principles as for the primary analysis, to evaluate the robustness of the results.
- In the case of premature treatment discontinuation not due to treatment intolerance and if the closest centralized assessment (Type 2) from the end of treatment did not confirm a stabilization or a worsening of the target IH, 50% of the patients concerned in each treatment group were selected at random and their complete or nearly complete recovery at W24 was redefined as a success. A sensitivity analysis of the redefined primary endpoint was carried out on the ITT data set, based on the same principles as for the primary analysis.
- An analysis of the primary endpoint (on ITT and PP data sets) using an extension of the combination test for logistic regression. The logistic regression model was adjusted for the stratification factors and randomization ratio.

Other secondary and exploratory efficacy endpoints

- W24 analysis and key secondary endpoint of W96 analysis:
  Other secondary and exploratory efficacy endpoints were analyzed on the ITT data set.
  All endpoints were analyzed descriptively and, where applicable, inferential analyses were performed using the same principles as those described for the primary endpoint.
  - W24 and W96 analyses:
    Standard procedures (for example, Kaplan Meier analyses for time-to-event endpoints) were also used to analyse the endpoints.
  All efficacy endpoints were described by treatment group on the ITT data set with overrun.
### Statistical methods (continued):

#### Safety analyses

Descriptive analyses of the safety endpoints were carried out on the Safety data set.

**AEs:**
- Number (N) (%) of patients by System Organ Class (SOC) and Preferred Term (PT) of MedDRA with at least one: treatment-emergent AE (TEAE), serious AE (SAE), AE leading to a study treatment discontinuation, moderate TEAE, severe TEAE, drug-related* TEAE (*suspected or insufficient data), TEAE with an outcome “Not recovered”, “is recovering” or missing, TEAE by minimal onset time,
- Tabulated individual data for SAEs, AEs leading to definitive study treatment discontinuation, AE with an outcome “recovered with sequelae” and AE with an outcome “unknown”, TEAE linked to bronchospasm, TEAE linked to cardiovascular disorder,
- N (%) of patients by SOC and PT of MedDRA with at least one: non TEAE pre-treatment, non TEAE post-treatment
- N (%) of patients with either a TEAE linked to bronchiolitis or bronchospasm;

**ECG:**
- For PR, HR, QTc-Bazett (QTcB), QTc-Fridericia (QTcF) and QTc-Pediatric (QTcP), values, changes from predose and changes from baseline over time,
- N (%) of patients by CHMP categories of QTcB, QTcF, QTcP values and changes from baseline,
- Individual data listing for patients with ECG with anomalies considered as non safe to continue treatment;

**2-dimensional cardiac ultrasound evaluation:** Descriptive statistics over time;

**Vital Signs:**
- Values, changes from predose and changes from baseline over time,
- Qualitative analyses relative to normal ranges: N (%) over time,
- N (%) of patients with low and very low values relative to a more stringent categorization (used by the IDMC) of blood pressure (SBP/DBP), HR and glycermia and referred to as ‘potentially clinically significant values (PCSVs)’ for SBP/DBP and HR.

**Laboratory data:**
- Descriptive statistics for values and changes over time,
- Qualitative analyses relative to normal ranges: N (%) over time,
- Tabulated individual data listing for patients with out of range values issued from local laboratories and from literature;

**Neurodevelopment assessment:** Descriptive statistics over time;

**Concomitant Treatments:** Frequencies of use by WHO-DRUG ATC classes.
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Name of finished product: Referring to Module 5 of the Dossier

Name of active substance: Vol.: ......Page: ......

Summary - Conclusions:

Patients’ disposition and data sets

**W24 analysis:**

512 patients were screened of whom 460 were randomized and 456 were treated; 323 completed the W24 treatment period. The highest rate of premature treatment discontinuation was observed in the placebo arm (65.5%), intermediate rates were observed in the propranolol 3 months regimen groups (36.4% and 35.6% in the 1 and 3 mg/kg/day arms, respectively), and the lowest rates were observed in the propranolol 6 months regimen groups (14.6% and 13.7% in the 1 and 3 mg/kg/day arms, respectively).

Distribution of patients according to randomization, W24 completion and the various analyzed populations is presented below:

<table>
<thead>
<tr>
<th>Randomized</th>
<th>Placebo (N = 55)</th>
<th>V0400SB 1 mg/kg/day 3mths (N = 99)</th>
<th>V0400SB 1 mg/kg/day 6mths (N = 103)</th>
<th>V0400SB 3 mg/kg/day 3mths (N = 101)</th>
<th>V0400SB 3 mg/kg/day 6mths (N = 102)</th>
<th>Total (N = 460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W24 completers</td>
<td>19</td>
<td>63</td>
<td>88</td>
<td>65</td>
<td>88</td>
<td>323</td>
</tr>
<tr>
<td>Safety (= all patients treated = ITT with overrun)</td>
<td>55</td>
<td>98</td>
<td>102</td>
<td>100</td>
<td>101</td>
<td>456</td>
</tr>
<tr>
<td><strong>Efficacy Stage 1+Stage 2</strong></td>
<td><strong>Placebo</strong></td>
<td><strong>V0400SB 1 mg/kg/day 3mths</strong></td>
<td><strong>V0400SB 1 mg/kg/day 6mths</strong></td>
<td><strong>V0400SB 3 mg/kg/day 3mths</strong></td>
<td><strong>V0400SB 3 mg/kg/day 6mths</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td>55*</td>
<td>41</td>
<td>40</td>
<td>39</td>
<td>101*</td>
<td>276</td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td>53</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>93</td>
<td>259</td>
</tr>
<tr>
<td><strong>ITT-Stage 1</strong></td>
<td>25</td>
<td>41</td>
<td>40</td>
<td>39</td>
<td>43</td>
<td>188</td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td><strong>Overrun treated patients</strong></td>
<td>0</td>
<td>57</td>
<td>62</td>
<td>61</td>
<td>0</td>
</tr>
</tbody>
</table>

* Note that these two arms were the only compared together for the primary efficacy analysis.

Overall, randomization strata and other baseline characteristics were well balanced between randomization arms. Overall, 71.3% of patients were female, the mean (sd) age was 103.9 (31.0) days, with 36.6% in the 35-90 days age group and 63.4% in the 91-150 days age group; 26.8% of patients had been born prematurely; 2.6% had been more than 2 months premature. The prematurity rate ranged between 21.6% (1 mg/kg/day 3 months arm) to 34.5% (placebo arm). The mean (sd) birth weight was 3.01 (0.74) kg.

The mean age at the onset of the IH was 15.5 days; 69.7% of patients had a facial target IH; 89.0% of patients had localized target IH, 5.5% had a segmental IH and 5.5% IHs had an indeterminate subtype of target IH.

Among the 460 randomized patients, 137 prematurely discontinued the randomized treatment. Nearly 2/3 of the patients (36/55: 65.5%) in the placebo arm versus 36.4% (1 mg/kg/d 3 months), 35.6% (3 mg/kg/d 3 months) 14.6% (1 mg/kg/d 6 months) and 13.7% (3 mg/kg/d 6 months) in the active arms. Treatment discontinuations occurred early in the placebo arm (49.1% of the patients had discontinued treatment at W5), later in the two 3 months active treatment arms (after W12) and without any particular pattern in the two 6 months active treatment arms.

Treatment inefficacy was the more frequent primary reason in all arms, but with rates different between arms: higher in the placebo arm (32/55 patients, 58.2%), intermediate in the two 3 months duration arms: 30/99 patients (30.3%) in the 1 mg/kg/d 3 months arm and 25/101 patients (24.8%) in the 3 mg/kg/d 3 months arm and lower in the two 6 months duration arms: 7 patients (6.8%) in the 1 mg/kg/d 6 months arm and 9 patients (8.8%) in the 3 mg/kg/d 6 months arm.

**W96 analysis:**

Randomized | Placebo (N = 55) | V0400SB 1 mg/kg/day 3mths (N = 99) | V0400SB 1 mg/kg/day 6mths (N = 103) | V0400SB 3 mg/kg/day 3mths (N = 101) | V0400SB 3 mg/kg/day 6mths (N = 102) | Total (N = 460) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT with overrun</td>
<td>33</td>
<td>98</td>
<td>102</td>
<td>100</td>
<td>101</td>
<td>456</td>
</tr>
<tr>
<td>Entered the follow-up period (W96 Safety set)</td>
<td>85</td>
<td>91</td>
<td>87</td>
<td>95</td>
<td>391</td>
<td></td>
</tr>
<tr>
<td>Had completed the 24-week study treatment period</td>
<td>19</td>
<td>60</td>
<td>85</td>
<td>65</td>
<td>87</td>
<td>316</td>
</tr>
<tr>
<td>Were in success at W24</td>
<td>2</td>
<td>8</td>
<td>50</td>
<td>12</td>
<td>61</td>
<td>133</td>
</tr>
</tbody>
</table>

CSR - Final Version: May 5, 2014 11/2100
Efficacy results

**Interim analysis results**

The interim analysis was conducted on the 188 ITT Stage 1 patients. The efficacy results clearly favored the 3 mg/kg/day 6 months arm with 62.8% complete or nearly complete resolution versus 8.0% (2 patients) in the placebo arm (and 9.8% in the 1 mg/kg/day 3 months arm, 37.5% in the 1 mg/kg/day 6 months arm and 7.7% in the 3 mg/kg/day 3 months arm). On the basis of these efficacy results, and of the favorable safety results, the IDMC recommendation was to continue the trial, with the 3 mg/kg/day 6 months arm and the placebo arm, without sample size adjustment/re-estimation.

**W24 efficacy analysis results**

Primary efficacy analysis:

At the end of the second stage, 55 patients in the placebo arm and 101 in the 3 mg/kg/day 6 months arm were analyzed in the ITT data set. 2 patients (3.6%) in the placebo arm and 61 patients (60.4%) in the active arm presented complete or nearly complete resolution of their IH between baseline and week 24. The combined p value (<0.0001) showed that the difference was highly statistically significant (at the chosen 0.005 level). The observed difference in rates of complete/nearly complete resolution (60.4% vs. 3.6%) was larger than the hypotheses used in the protocol to compute sample size (55% vs. 10%). The results are consistent between the two stages.

<table>
<thead>
<tr>
<th>Primary endpoint - ITT</th>
<th>Placebo (N = 55)</th>
<th>V0400SB 3 mg/kg/day 6mths (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall/combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/missing</td>
<td>55 / 0</td>
<td>101 / 0</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (3.6%)</td>
<td>61 (60.4%)</td>
</tr>
<tr>
<td>No</td>
<td>53 (96.4%)</td>
<td>40 (39.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary endpoint - PP</th>
<th>Placebo (N = 53)</th>
<th>V0400SB 3 mg/kg/day 6mths (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall/combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/missing</td>
<td>53 / 0</td>
<td>93 / 0</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.9%)</td>
<td>56 (60.2%)</td>
</tr>
<tr>
<td>No</td>
<td>52 (98.1%)</td>
<td>37 (39.8%)</td>
</tr>
</tbody>
</table>

Other analyses of primary endpoint:

Results on the PP population were consistent with those in the ITT population (60.2% vs. 1.9%). Adjusted analyses of the primary endpoint on both the PP and ITT analyses also demonstrated superiority of the 3 mg/kg/day, 6 months arm.

The sensitivity analysis confirmed the results of the primary analysis (significant superiority of the active treatment arm) despite the relaxation of the definition of failures resulting in a high increase of the success rate in the placebo arm (from 2 patients to 15: 3.6% to 27.3%) when only one additional patient in the active treatment arm was considered a success.

No differences in effect between facial and non-facial hemangioma were observed. Treatment effect magnitude (placebo adjusted effect) was similar between the two age strata, but crude rates of resolution were slightly higher in the younger stratum, a potential indication that early treatment during the proliferative phase could be beneficial. No evidence of differences in results between the two stages of the adaptive design was observed.
Efficacy results (continued):

Analyses of secondary endpoints:
With respect to secondary endpoints, improvement (on centralized assessment) occurred early in the 3 mg/kg/day 6 months arm during treatment, with 88.0% improvement (and 1.0% worsening) at W5 vs. 5.4% (and 10.8% worsening) in the placebo arm. Sustained improvement (i.e., maintained at each subsequent visit) occurred early in the 3 mg/kg/day 6 months arm, with 72.7% of the patients showing sustained improvement at W5.

Similar results on improvement and time to first sustained improvement of the IH were observed for on-site investigators’ and parents’/guardians’ assessment. The observed difference between the results of the primary endpoint from central readers’ and investigators’ assessments could be explained by the non-comparable assessment conditions.

A significantly greater reduction in target IH surface and target IH color was achieved in the 3 mg/kg/day 6 months arm. A greater reduction in the maximal diameter was also observed, but it was not statistically different from the reduction in the placebo arm.

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoints</th>
<th>Placebo (N = 55)</th>
<th>V0400SB 3 mg/kg/day 6mths (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralized quantitative assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in surface area at W24 compared to baseline (cm²)</td>
<td>0.464 (1.804)</td>
<td>-1.207 (2.439)</td>
</tr>
<tr>
<td>Change in maximal diameter at W24 compared to baseline (cm)</td>
<td>-0.028 (0.743)</td>
<td>-0.179 (0.731)</td>
</tr>
<tr>
<td>Change in color at W24 compared to baseline (dE*2000)</td>
<td>-0.054 (4.824)</td>
<td>-7.369 (7.430)</td>
</tr>
<tr>
<td>Centralized qualitative assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First sustained improvement at W5</td>
<td>5.4%</td>
<td>72.7%</td>
</tr>
<tr>
<td>KM rate*</td>
<td>9.0%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Investigator’s on site assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.5%</td>
<td>26.7%</td>
</tr>
<tr>
<td>First sustained improvement at W5</td>
<td>20.1%</td>
<td>70.9%</td>
</tr>
<tr>
<td>KM rate*</td>
<td>32.4%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Parents’ on site assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19.9%</td>
<td>67.4%</td>
</tr>
<tr>
<td>First sustained improvement at W5</td>
<td>45.0%</td>
<td>85.6%</td>
</tr>
</tbody>
</table>

* KM rate = Kaplan-Meier cumulative incidence estimate; † calculated on time to first sustained improvement assessed at D0, D7, D14, D21, W5, W8, W12, W16, W20, W24; ‡ calculated on time to first sustained improvement assessed at D0, D7, D14, D21, W5, W8, W12, W16, W20, W24. NS=Non statistically significant.
Efficacy results (continued):

**W96 efficacy analysis results**

- **Key secondary efficacy endpoint**: the rate of complete resolution of target IH without sequelae or with minimal sequelae at W48 as compared to baseline according to the Investigator’s assessment was 1.8% (1 patient) in the placebo arm and 7.9% (8 patients) in the 3 mg/kg/day 6 months arm (p=0.14).

- As noted in the W24 analysis, on site Investigator’s assessment of complete/nearly complete resolution showed less discriminating results than the centralized assessment of complete/nearly complete resolution due to non-comparable assessment conditions. Hence, the most relevant efficacy results during the follow-up period should be based on the analyses of the centralized type I assessment at W96 (and derived success as defined per protocol) and of IH treatment intake during the follow-up period in the patients from the 3 mg/kg/day 6 months and placebo arm of the ITT with overrun population and in pertinent subgroups of this population:

  - Considering patients with type I (complete/nearly complete) assessment available at W96 and considering patients who did not enter the follow-up period but took any IH treatment from W24, 42 patients (out of 84; 50.0%) had complete/nearly complete resolution in the placebo arm; 42 patients (out of 84; 50.0%) had complete/nearly complete resolution in the 3 mg/kg/day 6 months arm.

  - Out of 54 patients from the 3 mg/kg/day 6 months arm achieving success at W24 (primary endpoint), who entered the follow-up period, and with success assessment available at W96, 35 (64.8%) achieved success at W96 without any additional treatment for their IH over the follow-up period (i.e., sustained response). In the placebo arm, the 2 patients with spontaneous remission achieved at W24 had a sustained response at W96;

  - Among the patients who entered the follow-up period, with type I efficacy assessment available at W96, and considering W96 complete/nearly complete resolution as success even in the patients with new IH treatment intake (10 cases in the 3 mg/kg/day 6 months arm and 7 in the placebo arm), the success rates raise to 52/79 (65.8%) in the 3 mg/kg/day 6 months arm and 16/28 (57.1%) in the placebo arm;

  - Out of the 61 patients from the 3 mg/kg/day 6 months arm with success at W24 (primary endpoint) and who entered the follow-up period, only 7 (11.5%) required re-initiation of IH treatment over the W24-W96 follow-up period (of whom 6 [9.8%] required re-initiation of systemic IH treatment), confirming that the successful results obtained at W24 were sustained after treatment discontinuation.

- **Time-to-sustained event analyses** should be described and interpreted cautiously, because of the difference between regimen arms on the follow-up of patients: In Kaplan Meier analyses, the censoring should be independent from the regimen group. In this study, the number of patients entering the follow-up is clearly lower in the placebo arm (53/55, 60%) than in the 3 mg/kg/day 6 months arm (95/102, 93.1%). Moreover, for patients entering the follow-up, the number of patients with intake of prohibited treatment for IH after EOT is also relatively different: 16/33 in placebo arm (48.5%) versus 21/95 in the 3 mg/kg/day 6 months arm (22.1%). Of note, if a patient was not entering in the follow-up period and did not take any prohibited treatment, this patient was censored for the analysis of time to first event related to resolution of the target IH. Consequently, the censoring is clearly dependent from the regimen group and as independence does not hold, the estimates are biased and may be inaccurate. Despite this bias responsible for artificially better results in the placebo arm, a consistent trend towards better "survival curves" for the 3 mg/kg/day 6 months was observed on all endpoints analyzed.
Confidential V00400 SB 2 01

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</table>

Safety results

**W24 safety analysis**

**Serious adverse events:**

No death was reported during the study treatment period.

Thirty three (33) SAEs were reported in 26 patients. Five SAEs were considered as treatment related either by the Investigator or by the Sponsor. Four SAEs were reported as suspected unexpected serious adverse reactions: one AE of worsening of IH in the placebo arm; one AE of AV block in the 1 mg/kg/day 3 months; one AE of ulceration of IH and one AE of obstructive bronchitis in the 3 mg/kg/day 3 months. One SAE was expected (bradycardia in a context of non related enterocolitis). All 5 SAEs were resolved with corrective treatment except the AV block (spontaneously resolved). The study treatment was definitely discontinued in 4 patients and temporarily in 1 patient (bronchitis). No treatment-related SAE was reported in the 6 months propranolol arms.

**Adverse events:**

**TEAEs** were reported in 406 of 456 patients: in fewer patients in the placebo arm (40 patients [72.7%]) than in the four active arms where it was observed no obvious differences between the 1 and 3 mg/day regimens or between the 3 months and 6 months regimen (89 patients [90.8%] in the 1 mg/kg/day 3 months arm, 90 patients [88.2%] in the 1 mg/kg/day 6 months arm, 91 patients [91.0%] in the 3 mg/kg/day 3 months arm, and 96 patients [95.0%] in the 3 mg/kg/day 6 months arm). These differences in TEAE incidences are explained, at least partly by the imbalances between the extents of treatment exposure due to premature treatment discontinuation in the placebo arm (about half the exposure to study treatment as compared to active treatment arms).

The most frequent TEAEs were either:

- **non specific events** frequently occurring in infant (nasopharyngitis, pyrexia, teething, bronchitis, vomiting, upper respiratory tract infection, cough, gastroenteritis, diaper dermatitis, toothache, conjunctivitis, vaccination complication), more frequently reported in the active regimen arms. For these events, the differences in occurrence between the active arms and placebo were mainly linked to higher frequencies in the active arms over the W12-W24 period, where fewer placebo patients were still exposed to the study treatment. There was no clear dose-dependence for these events, except for bronchitis (11 of 200 [5.5%] patients vs. 23 of 201 [11.4%] patients when comparing the 1 mg/kg/day regimens to the 3 mg/kg/day regimens, up to W12 in the 3 months regimens and up to W24 in the 6 months regimens);

- **or known propranolol adverse reactions:** diarrhea for the most frequent, sleep disorders (sleep disorder, middle insomnia, insomnia, nightmares, poor quality sleep), other CNS disorders (hypersomnia and irritability), and peripheral coldness. For these events a higher frequency in the active treatment arms was observed during the early periods (titration and D21-W12). Accordingly, these events were the most frequent TEAEs reported as related to the study treatment. There was no clear dose-dependence for these events, except for diarrhea, (28 of 200 [14.0%] patients vs. 44 of 201 [21.9%] patients when comparing the 1 mg/kg/day regimens to the 3 mg/kg/day regimens, up to W12 in the 3 months regimens and up to W24 in the 6 months regimens). Neither diarrhea TEAEs were of severe intensity, led to prematurely treatment discontinuation or were reported as SAEs.

**Grouped events potentially linked to bronchospasm or bronchiolitis** (or more generally bronchial hyperreactivity symptoms including bronchiolitis): there was a trend to dose-dependence for these events (12 of 200 [6.0%] patients vs. 19 of 201 [9.5%] patients when comparing the 1 mg/kg/day regimens to the 3 mg/kg/day regimens, up to W12 in the 3 months regimens and up to W24 in the 6 months regimens). Neither diarrhea TEAEs were of severe intensity, led to prematurely treatment discontinuation or were reported as SAEs.

**Cardiovascular events of clinical interest** were rare and asymptomatic: expected bradycardia was reported in only two patients [one of the 1 mg/kg/day 6 months arm (on D167) and one of the 3 mg/kg/day 3 months arm (on D7)]. The SAE of AV block of second degree (Mobitz I type) was reported at D0 (after 1st drug intake) in one patient of the 1 mg/kg/day 3 months arm in whom suspicion of pre-existing cardiac disease was later identified on a post-treatment Holter monitoring.

**AE of hypoglycemia** was reported in only two patients, one in the 1 mg/kg/day 6 months arm and 1 in the 3 mg/kg/day 6 months arm. The glycemia was low in both cases on D14 (2.5 mmol/l and 2.9 mmol/l, respectively) and was normalized at each other time points. None was symptomatic.
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**Name of finished product:** Referring to Module 5 of the Dossier  
**Name of active substance:** Vol.: ......Page: ......  

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<tr>
<th>Safety results (continued):</th>
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<tbody>
<tr>
<td><strong>AEs leading to premature treatment discontinuations:</strong> 22 patients discontinued the study treatment due to an AE, more frequently in the placebo arm (10.9%), than in the two 3 months duration arms (4.1% and 7.0%), and more frequently in the two 3 months duration arms than in the two 6 months duration arms (2.0% and 3.0%). Most frequent AEs having led to premature discontinuation were events linked to lack of efficacy (drug ineffective or condition aggravated: 4 of 7 cases in the placebo arm, 1 of 4 cases in the 1 mg/kg/day 3 months arm, none of 2 cases in the 1 mg/kg/day 6 months arm, 2 of 10 cases in the 3 mg/kg/day 3 months arm and 1 of 3 cases in the 3 mg/kg/day 6 months arm).</td>
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<thead>
<tr>
<th>Vital signs and ECG findings:</th>
</tr>
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<tbody>
<tr>
<td>The findings observed on cardio-vascular and ECG parameters were expected: decreased mean blood pressure (SBP and DBP), heart rate (HR), and increased PR, linked to the beta-blocking effect of propranolol. This occurred in the four active arms (without evidence of a clear difference between the 1 and 3 mg/kg/day arms) mainly during the first weeks of treatment, the difference vs. placebo decreasing from W5-W8 to disappear at W24.</td>
</tr>
<tr>
<td>High incidences of SBP, DBP, or HR measures below the normal range were observed in all arms including the placebo arm (41.8% in the placebo arm, 50.0% to 53.5% in the active arms for SBP; 89.1% in the placebo arm, 87.3% to 97.0% in the active arms for DBP; 14.6% in the placebo arm, 15.7% to 25.7% in the active arms for HR). However, very few cardio-vascular vital sign values below the normal range were considered as clinically significant by the Investigator and led to the reporting of an AE: hypotension or low BP in 6 patients of whom 5 on propranolol (3 patients from a 1 mg/kg/day regimen arm, and 2 patients from a 3 mg/kg/day regimen arm during the titration phase), and bradycardia in 2 patients (1 patient from a 1 mg/kg/day regimen arm, and 1 patient from a 3 mg/kg/day regimen arm during the titration phase). Almost all events were isolated, and all corresponding values returned to normal.</td>
</tr>
<tr>
<td>There was no clear treatment effect regarding frequencies of very low blood pressure potentially clinically significant values (very low PCSVs; &lt; 50/30 mmHg) and low heart rate PCSVs (&lt; 60 bpm) that mainly occurred during the titration period. Indeed, blood pressure very low PCSVs were observed in 8 of 55 [14.5%] patients in the placebo arm, 14 of 200 [7.0%] patients in the 1 mg/kg/day regimens and 29 of 201 [14.4%] patients in the 3 mg/kg/day regimens during the D7-1h-D14-4h period (i.e., the period with dose increments in the 3 mg/kg/day arms), and very few patients had low heart rate PCSVs (1 of 55 [1.8%] patients in the placebo arm, 2 of 200 [1.0%] patients in the 1 mg/kg/day regimens, and 5 of 201 [2.5%] patients in the 3 mg/kg/day regimens during the whole study period from D0-1h). These cardio-vascular PCSVs were generally isolated.</td>
</tr>
<tr>
<td>QTc analyses did not show any repolarization concerns on propranolol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With regards to evolution over time in biological parameters the only trends observed were expected changes in this newborn/infant population. No particular trends in abnormal laboratory values or clinically significant abnormal laboratory values were noticed.</td>
</tr>
</tbody>
</table>

**Post-study treatment safety analysis**

**Serious adverse events:**

No death was reported over the study follow-up period. Forty six (46) post-treatment SAEs were reported in 28 (7.2%) patients with a higher incidence in the placebo arm (5 patients, 15.2%); 8 SAEs occurring in 5 patients were systemic beta-blocker-emergent. The most frequent PTs (at least 2 events) were: Bronchiolitis (5 SAEs in 4 patients, 3 of which in 2 patients were beta-blocker-emergent), Gastroenteritis (4 SAEs in 2 patients, none was beta-blocker-emergent), Rotavirus infections (4 cases in 4 patients including 1 case of Gastroenteritis rotavirus; none was beta-blocker-emergent), Pneumonia (3 cases in 3 patients, none was beta-blocker-emergent), Surgery for IH removal (2 cases in 2 patients, none was beta-blocker-emergent), Bronchitis (2 cases in 2 patients, none was beta-blocker-emergent), Hip Surgery (2 cases in 1 patient, for Hip dysplasia) and Convulsions (2 cases in 2 patients, including 1 case of Febrile convulsion, none was beta-blocker-emergent). |

**Adverse events:**

The analysis of adverse events having occurred during the post-study treatment follow-up period presents limitations related to the heterogeneity of the population concerned and small sample sizes of groups according to their previous treatment during the “W24” period and to their intake or not of beta-blockers during the follow-up period. The following results are presented in the overall population having entered the follow-up period and in the population having received beta-blockers during this period.
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Safety results (continued):

Among the 391 patients who entered the follow-up period, the most frequently reported AEs (in 10% or more of the patients) were Nasopharyngitis (175 events in 109 patients, 27.9%), Pyrexia (149 events in 86 patients, 22.0%, including 1 SAE), Bronchitis (111 events in 68 patients, 17.4%, including 2 SAEs), Ear infection (130 events in 64 patients, 16.4%, including 1 SAE), Upper respiratory tract infection (84 events in 51 patients, 13.0%), and Gastroenteritis (56 events in 50 patients, 12.8%, including 4 SAEs). All are non specific events, frequently occurring in infants and children.

There were 106/391 (27.1%) patients treated with systemic beta-blockers during the follow-up period.

The most frequent systemic beta-blocker emergent AEs, reported in 10% or more of the patients were Nasopharyngitis (36 events in 28 patients, 26.4%), Upper respiratory tract infection (27 events in 15 patients, 14.2%), Pyrexia (26 events in 17 patients, 16.0%), Bronchiolitis (18 events in 13 patients, 12.3%), Bronchitis (15 events in 13 patients, 12.3%), Gastroenteritis (12 events in 12 patients, 11.3%), Ear infection (23 events in 11 patients, 10.4%), and Diarrhea (13 events in 11 patients, 10.4%).

No new safety signal was identified in patients receiving systemic beta-blockers during the follow-up period.

Among the 391 patients who entered the follow-up period, the events potentially linked to either bronchiolitis and/or bronchospasm were reported in 49 patients (12.5%), more frequently in the propranolol previously treated arms, particularly the 3 mg/kg/day 6 months arm (6.1%, 95%CI [0.7%, 20.2%]) in the placebo arm, 9.4% in the 1 mg/kg/day 3 months arm, 11.0% in the 1 mg/kg/day 6 months arm, 12.6% in the 3 mg/kg/day 3 months arm and 18.9%, 95%CI [11.6%, 28.3%] in the 3 mg/kg/day 6 months arm). The two CIs do overlap and there is no definitive evidence of a statistically significant difference in rates of events potentially linked to either bronchiolitis and/or bronchospasm between the placebo and the 3 mg/kg/day 6 months arm. Excluding the cases of bronchospasms reported in children with intercurrent episodes of bronchiolitis, which might be attributed to the underlying condition, 16 cases of bronchospasm (4.1%) remain to be interpreted. Considering these 16 cases, there was no evidence in favour of a dose relationship, with cases equally distributed between the 1 mg/kg/day and 3 mg/kg/day doses: 2 cases (2.4%) were reported in children of the 1 mg/kg/day 3 months arm, 2 (2.3%) were reported in the 3 mg/kg/day 3 months arm, and 6 cases were reported in each of the 6 months treatment arms (i.e., 6.6% and 6.3% in the 1 mg/kg/day 6 months and 3 mg/kg/day 6 months arms, respectively). In only 3 cases (one in the 1 mg/kg/day 3 months arm, one in the 1 mg/kg/day 6 months arm and one in the 3 mg/kg/day 6 months arm), bronchospasms were reported with no documented intercurrent or historical condition or treatment that might contribute to explain these 3 cases. Considering these small numbers, together with the absence of any published evidence of bronchial hyperreactivity associated with previous beta-blocker use, no definite conclusion can be drawn.

Cardiovascular events were very rare, with one single report of Bundle branch block right in 1 patient of the 1 mg/kg/day 3 months arm (not systemic beta-blocker emergent), 2 reports of Supraventricular extrasystoles (one being systemic beta-blocker emergent) in 1 patient of the 1 mg/kg/day 6 months arm and 1 report of Aortic dilatation in 1 patient of the 1 mg/kg/day 6 months arm (not systemic beta-blocker emergent).

AEs related to hypoglycemia: one event coded Blood glucose decreased was reported in 1 patient of the 1 mg/kg/day 3 months arm (not systemic beta-blocker emergent), 1 event coded Hypoglycemia was reported in 1 patient of the 1 mg/kg/day 3 months arm (systemic beta-blocker emergent) and one event coded Hypoglycemic unconsciousness was reported in 1 patient of the 1 mg/kg/day 3 months arm due to the administration of systemic beta-blocker in fasting conditions.
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Safety results (continued):

Vital signs, ECG and Cardiac ultrasound findings:

General trends in vital signs and ECG findings were observed that correspond to expected changes in the age range of the included patients: increase in SBP/DBP, decrease in HR (both at physical exam and ECG), decrease in respiratory rate. There was no evidence of any between-arm difference in vital signs or ECG findings linked to the treatment received during the treatment phase. In patients treated with systemic beta-blockers, the expected effects were observed: a decrease in blood pressure (both SBP and DBP), a decrease in HR and an increase in PR and in QTcP.

Only one QTcP value above 450 ms was recorded (on W48, a value of 456.9 ms, observed in one patient not receiving beta-blockers during the follow-up period, and who had normal QTcP measures at all the other study visits, before and after this elevated value).

The mean Left Ventricular Ejection Fraction (LVEF) measured by cardiac ultrasound at EoS was 68.7% overall, without evidence of between-arm differences or of differences between patients receiving systemic beta-blockers or not.

Physical exam:

As expected in the age range of included patients, height, weight, head circumference and body surface area increased over the study period, with no evidence of any difference between randomized arms or between patients receiving systemic beta-blockers or not over the follow-up period.

Neurodevelopmental assessment:

Seven patients (7/391, 1.8%) had a report of abnormal neurodevelopmental assessment at the end of the follow-up period. All had been treated with propranolol during the treatment period (7/322 [2.17%], 95% CI: [0.8%, 4.4%]) and none with placebo (0/29, 95% CI: [0.0%, 11.9%]); the overlap of the CIs does not allow to draw any meaningful conclusion as to the relative risk between placebo and propranolol previous treatment. The observed incidence is consistent with incidences reported in the literature in the general population. Only two patients with a normal neurodevelopmental assessment at screening and no pre-existing risk factors were diagnosed with a slight delayed psychomotor development (speech/walking). However, the chronology is not suggestive of a causal relationship between the onset of the AEs and propranolol. There was no evidence of an increased incidence of abnormal neurodevelopmental assessment in patients treated with Propranolol as compared to placebo. No signal has been raised concerning a potential risk on neurodevelopment associated with the use of propranolol in infants.

Safety conclusion:

Considering all the safety data observed during the study, there was:

- During the 24-week study treatment period:
  - no unexpected safety signal related to propranolol,
  - no obvious dose dependence for adverse effects except for bronchial hyperreactivity and diarrhea, without severe consequences for the patients,
  - very few cardiovascular effects with no obvious dose dependence in the tested range.

- During the long-term post-treatment follow-up period (up to W96):
  - Within the limitations linked to the heterogeneity of the population and small sample sizes, there was no evidence of any long term safety impact of the initial 12- or 24-week treatment with propranolol. A slight increase in the incidence of bronchospasm events in the propranolol previously treated patients was observed. No effect on the patients’ growth, neurodevelopment, cardiovascular parameters or glycemia was detected.

Conclusion:

This double-blind clinical study compared four regimens of propranolol (1 and 3 mg/kg/day for 3 or 6 months each) to placebo for 6 months in the treatment of proliferating IH requiring systemic therapy in infants (aged 35-150 days at initiation), using an objective primary efficacy endpoint based on blinded centralized photographic assessment.

The results demonstrate that, in the treatment of IH, the study propranolol oral solution at the dose of 3 mg/kg/day for 6 months induces a rapid improvement, a highly significant efficacy level at W24, and a sustained response up to 72 weeks after the end of treatment, with only a minority of patients requiring re-treatment with systemic IH therapy.

There was no unexpected safety signal with any of the propranolol dose regimens administered, and no effects on the cardiovascular or metabolic systems or on the child’s growth and neurodevelopment were detected.

Date of Report: May 5, 2014
Pierre Fabre Dermatologie  
Represented by: Institut de Recherche Pierre Fabre (IRPF)  
45, Place Abel Gance  
F-92100 Boulogne

1. TITLE PAGE

CLINICAL STUDY REPORT

A multicentre, open-label study of propranolol in infants with proliferating infantile hemangioma requiring systemic therapy

Investigational product: V0400SB / oral solution / 2 or 3 mg/kg/day

Study Design: Multicenter, uncontrolled, open label study

EudraCT number: 2010-023488-16

Protocol number: V00400 SB 3 01

Phase of development: III

Date of first enrolment: April 12, 2011

Date of last completed: December 12, 2013

Coordinating Investigator: Christine Léauté-Labrèze, MD  
CHU de Bordeaux, F-33000 BORDEAUX  
Phone: +33 (0)5 56 79 59 42

Sponsor Representative for Study Report: Head of Clinical Development: François Brackman, MD  
IRPF, 3 avenue Hubert Curien, F-31100 TOULOUSE  
Phone: +33 (0)5 34 50 63 28

Date of report: June 12, 2014

Study performed in compliance with Good Clinical Practice.

This information may be disclosed in whole or in part, submitted for publication, or form the basis for an industrial property licence only with the written approval of Pierre Fabre Médicament.  
Pierre Fabre Médicament is the owner of this report.
2. SYNOPSIS

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<td>A multicentre, open-label study of propranolol in infants with proliferating infantile hemangioma requiring systemic therapy.</td>
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<td>Coordinating Investigator:</td>
<td>Christine Léauté-Labrèze, MD</td>
<td>CHU de Bordeaux, Hôpital Pellegrin Enfants, F-33000 Bordeaux</td>
</tr>
<tr>
<td>Principal Investigators:</td>
<td>Christine Léauté-Labrèze, MD</td>
<td>Smail Hadj-Rabia, MD</td>
</tr>
<tr>
<td>Study centers:</td>
<td>Two centers, both specialized in pediatric dermatology, recruited patients.</td>
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<td>April 12, 2011</td>
<td></td>
</tr>
<tr>
<td>(date of last completed)</td>
<td>December 12, 2013</td>
<td></td>
</tr>
<tr>
<td>Objectives:</td>
<td>The study objectives were:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- To allow the use of propranolol under adequate conditions of administration and follow-up in infants still requiring this systemic treatment (in the Investigator’s opinion) after their participation in one of two previous clinical trials (V00400 SB 1 02 and V00400 SB 2 01 [French centers]) of the same study drug (propranolol solution, coded V0400SB) in the treatment of the same target disease (IH);</td>
<td></td>
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<td></td>
<td>- To document in the included patients the study treatment safety profile (including the long-term post-treatment impact) and effect on the resolution of IH.</td>
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</tr>
<tr>
<td>Methodology:</td>
<td>The present study was conducted as an open-label uncontrolled study.</td>
<td></td>
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<tr>
<td></td>
<td>Included patients were treated with V0400SB at the dose of 2 or 3 mg/kg/day (at the Investigator’s discretion) for a period of up to 24 weeks (from D0 to W24, including a titration phase) and then followed up for a further period up to W96 (from the end of study treatment [W24/EOT] to W96/EOS [end of study]) off study treatment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients prematurely discontinued from the study treatment entered the follow-up period after the EOT and were followed up, up to W96/EOS.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Of note, for the patients who had participated in double-blind Study V00400 SB 2 01 (on-going at this study set up), the investigators were maintained blinded with respect to the treatment previously received (placebo, propranolol 1 mg/kg/day or 3 mg/kg/day).</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Visits:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The patient’s complete participation up to W24 (study treatment period) comprised 10 scheduled visits:</td>
<td></td>
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<tr>
<td></td>
<td>- A screening visit (when possible, the screening visit could be done on the same day as the baseline visit),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 9 visits during the 24-week study treatment period, starting on baseline visit (Day [D]0, 0 to 14 days after the screening visit, then D7, D14, D21 or Week [W]4*, W8, W12, W16, W20 and W24 (end of study treatment: EOT) (*amendment PA01).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The post-study treatment follow-up period consisted in 2 additional visits, on W48 and W96 (end of study: EOS).</td>
<td></td>
</tr>
<tr>
<td>Name of Company: Pierre Fabre Dermatologie</td>
<td>Name of finished product:</td>
<td>Name of active substance (or ingredient):</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Individual Study Table Referring to Module 5 of the Dossier</td>
<td>Vol.: .... Page: ......</td>
<td>(For National Authority Use Only)</td>
</tr>
</tbody>
</table>

**Number of patients (planned and analyzed):**
The number of patients was not predictable (part of the patients previously included in the concerned trials [V00400 SB 1 02 and V00400 SB 2 01]). 11 patients (in 2 centers) were included and participated in both study periods.

**Diagnosis and main criteria for inclusion:**
A patient was eligible for the study if he/she met all the following criteria:

- Who has received study treatment in studies V00400 SB 1 02 or V00400 SB 2 01 (French centers) and completed the corresponding end of study visit within the previous 6 months,
- For whom, written informed consent(s) for study participation has(have) been obtained from his/her Parent(s) or Guardian(s) prior to performing any study procedure,
- With Proliferating IH requiring systemic therapy with propranolol in the Investigator’s opinion,
- Who is registered with the French social security /or whose parent(s) or guardian(s) is(are) registered with the French social security.

**Test product**

<table>
<thead>
<tr>
<th>Doses</th>
<th>Mode of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol oral solution 3.75 mg/ml.</td>
<td>Administration of propranolol oral solution twice daily (morning and late afternoon around meal intake) for up to W24.</td>
</tr>
</tbody>
</table>
| 2 or 3 mg/kg/day (b.i.d, at the Investigator’s discretion) | **Titration procedure:**
- D0: 1 mg/kg/day
- D7: increase to 2 mg/kg/day
- D14: increase to 3 mg/kg/day (if judged necessary by the Investigator). |

**Batch numbers:**

- 2 batches of propranolol glass bottles were used:
  - batch SB0800, expiry date 04/2012,
  - batch SB0855, expiry date 08/2013.
- 1 batch of 5 ml pipettes: n°004849; expiry date: 03/2013

**Other product, dose, Mode of administration, Batch number:**

- Not applicable

**Duration of treatment:**

6-month treatment period (from D0 to W24, including a titration phase) in open conditions with the propranolol oral solution at a dosage of either: 2 mg/kg/day or 3 mg/kg/day b.i.d, at the Investigator’s discretion.

(Then further follow-up period up to W96, off study treatment)

**Reference therapy, dose, Mode of administration, Batch number:**

- Not applicable
Name of Company: Pierre Fabre Dermatologie

Name of finished product:

Referring to Module 5 of the Dossier

Name of active substance (or ingredient):

Vol.: ......Page: ......

Criteria for evaluation:

Efficacy: Target IH outcome measurements consisted of:

- Investigator’s qualitative assessments compared to baseline using a 4-point scale: complete resolution, improvement, stabilization, worsening;
- Target IH complications (cardiac impairment, eye impairment, ulceration, obstruction of visual axis, obstruction/stenosis of airway, hemorrhaging/bleeding) using a grading of 0-3 (for eye impairment and obstruction of visual axis, and of 0-5 for other complications);
- Invasive procedures (yes/no) carried out during the study for target IH.

Safety:

Adverse events: continuous assessment

Physical examination (height, weight, head circumference, pulmonary auscultation, liver palpation and global physical examinations): at each scheduled visit; Note that at D0 and each dose increase at D7 and possibly D14, the pulmonary auscultation was performed before and then every hour for 4 hours (±30 min) after the study drug administration.

Vital signs (temperature, heart rate, blood pressure, respiratory rate): at each scheduled visit. Note that at D0 and each dose increase at D7 and possibly D14, the vital signs were measured before and then every hour (±30 min) for 4 hours after the study drug administration.

Glycemia: on pin-pricks during up-titration.

ECG measurements: at screening, D0, D7, D14, possibly D21, W12, W24/EOT. Note that at D0 and each dose increase at D7 and possibly D14, the vital signs were measured before and then every 2 hours (±30 min) for 4 hours after the study drug administration.

Neurodevelopment evaluation (normal/abnormal) with respect to the Patient’s age was carried out by the Investigator at D0, W12, W24, W48 and W96. If the EOT visit was before W24, the neurodevelopment evaluation was performed at the EOT visit as well as at the W48 and W96 visits.

Statistical methods:

As a consequence of the low number of included patients (11 patients), no descriptive statistics were performed, only individual tabulated listings were provided. Those listings present raw data and some derived data.

Individual potentially clinically significant values and/or changes of vital signs, glycemia and QTcP (pediatric formula for QT correction) according to age were tabulated: blood pressure: < 60/40 mmHg (0-3 months of age), < 65/45 mmHg (3-6 months of age), < 70/50 mmHg (> 6 months of age), < 80/50 mmHg (>12 months of age), HR < 60 bpm (regardless of age), Glycemia < 2.6 mmol/l (regardless of age; QTcP > 480 ms or QTcP change from baseline > 60 ms (regardless of age).

Summary - Conclusions:

A total of 11 patients (in 2 centers: nos. 01 and 09) were treated: 6 patients prematurely discontinued the study treatment (5/6 for study treatment good efficacy, none for safety concerns).

All 11 patients entered the follow-up period and 1 patient prematurely withdrew from this period (loss to follow-up).

All patients but one had previously participated in study V00400 SB 201.

The 11 patients of the FAS (10 female and 1 male), were aged from 101 days to 397 days, with a weight ranging from 4.6 kg to 8.9 kg, and a head circumference ranging from 38 cm to 45.5 cm.

Seven (7) female patients were treated at 3 mg/kg/day (all from Center 01), and 4 patients (3 female and 1 male) were treated at 2 mg/kg/day (all from Center 09).
Efficacy results:

During the previous study (Study V00400 SB 1 02 in 1 case, Study V00400 SB 2 01 in 10 cases),

- 9 patients had prematurely discontinued the study treatment period of the previous study for inefficacy (5 while on placebo, one while on 1 mg/kg/day and 3 while on propranolol 3 mg/kg/day) and 2 patients had completed the planned treatment period on propranolol 3 mg/kg/day. Patients exclusively on placebo during the previous study (n=4) prematurely withdrew earlier (after 15-27 days) than the others (after 46-143 days);
- Paired successive visits comparisons on the target IH outcome showed:
  - No improvement in the patients having received only placebo (n=4), and several improvements from D7 in all the other patients;
  - Improvement of the IH at EOT in 3/4 patients withdrawn while on propranolol at 3 mg/kg/day. Stabilization with no previous improvement, or worsening of the IH at EOT in all the other patients.

During Study 301,

- The time interval before re-treatment was ≤ 3 days (7 patients), 14 days (1 patient), or > 10 weeks (3 patients);
  - 4 patients received the 2 mg/kg/day dosage (Center 09, of whom 2 previously exclusively on placebo) and 7 patients received the 3 mg/kg/day dosage (Center 01, of whom 2 previously exclusively on placebo);
  - A deep component of the target IH (mainly facial) was reported in 8/11 patients (of whom 6 received the 3 mg/kg/day dosage);
- 5 patients completed the study treatment period (of whom 3 previously exclusively treated by placebo) and 6 prematurely discontinued the study treatment period: 5 for good efficacy (of whom 3 previously treated by propranolol 3 mg/kg/day) and one (after 143 days of exposure at the 3 mg/kg/day dosage) due to empty bottles of study treatment;
- All patients completed the follow-up period except one (loss to follow-up from W48);
- During the study treatment period:
  - All had an improvement of their IH (as compared to baseline in the 7 patients who received the 3 mg/kg/day dosage, or since the previous visit in the 4 patients who received the 2 mg/kg/day dosage) from D7 (8/11), D14 (2/11) or W4 (1/11) and up to W24/EOT with a complete resolution at EOT (W20) in a patient who received 3 mg/kg/day (for a cumulative 27 weeks since the beginning of the previous [V00400 SB 2 01] study). Another patient, who received the 3 mg/kg/day dosage (for a cumulative 28 weeks since the beginning of the previous [V00400 SB 1 02] study) had also a complete resolution: at W16 which was sustained up to W96/EOS;
  - No complications of the IH were reported, and the 2 complicated IHs at baseline (ulceration in both cases: grade 1 and 3, respectively in 2 patients who both received the 3 mg/kg/day dosage) were normalized (grade 0): from Day 14 and W12, respectively.
- During the follow-up period,
  - There was no IH worsening (relative to baseline or the previous visit depending on the center / dosage received) except in one patient (the one with complete resolution at W20 on propranolol 3 mg/kg/day) and study treatment discontinuation on that day for good efficacy) who had a worsening at W24 (then improvement from W48). Two additional patients, both having received the 3 mg/kg/day dosage during the study treatment period (one treated in the previous study with 1 mg/kg/day and the other with 3 mg/kg/day) had a sustained complete resolution of their IH from W48;
  - No patients took systemic beta-blockers and 4 patients took a topical beta-blocker (generally one month after the EOT and for a duration of 2 months);
  - No complications of the IH were reported.
Safety results:
All the patients reported at least one AE: overall, 11 patients experienced 76 AEs. were mainly mild in severity.
Half the 76 AEs (38 TEAEs) were treatment-emergent, were mainly mild in severity (27/38) and no TEAEs led to study treatment definitive discontinuation. Twenty (20) TEAEs occurred in patients receiving 3 mg/kg/day (Center 01) and 18 TEAEs in patients receiving 2 mg/kg/day (Center 09). None of them were SAEs.
Among these 38 TEAEs,

- 3 events in the same patient (receiving 2 mg/kg/day) were severe: 2 led to temporary discontinuation of the study treatment (external ear inflammation, otitis media), and 1 (gastroenteritis) with no change; all recovered with corrective treatment,
- 2 events in another patient (receiving 2 mg/kg/day) were suspected by the Investigator to be related to the study treatment (decreased appetite and middle insomnia), both mild in severity, and both recovered without temporary discontinuation of the study treatment and without corrective treatment.

The most frequently experienced TEAEs were coded in the Infections and infestations SOC (23/38 events) and Gastrointestinal disorders (8/38 events).
The other half (38 FUPAEs/76 AEs) occurred during the follow-up period (W24/EOT to W96, off study treatment), all in Center 01 (6 patients previously treated at 3 mg/kg/day). They were mainly moderate in severity (27/38) and, as expected in this period, none were considered related to the study treatment by the Investigator.
All the 38 FUPAEs resolved with or without corrective treatment, except 2 events: asthma and nasopharyngitis in one patient (n°0501001). This patient experienced also the only SAE of the study (bronchiolitis) which occurred during the follow-up period (off study treatment). This follow-up SAE was severe in intensity, lasted 9 days and resolved with corrective treatment.
The most frequently experienced FUPAEs were coded in the Infections and infestations SOC (33/38 events).
No hypoglycemia (< 60 mg/dL, 3.33 mmol/L) was measured from pinpricks during the titration period.
All patients presented at least once a potentially clinically significant value (PSCV) of low SBP/DBP or HR, mostly of low DBP. No vital sign value was considered clinically significant by the Investigator. No clinically symptomatic bradycardia or hypotension was reported.
No ECG measurement (considered normal or abnormal by the Investigator) was considered clinically significant by the Investigator. With respect to QTcP evaluation according to CHMP classes, no QTcP was > 450ms and 6/11 patients had at least one change from baseline in QTcP by > 30 ms of whom 1 patient (receiving 2 mg/kg/day) had one change from baseline by > 60 ms (Day7 T4h).
No abnormalities in the children neurodevelopment were reported.

Conclusion:
- Within the limitation of the small sample size, there was no unexpected safety signal related to propranolol during the study treatment period (up to W24) and no evidence of any long term post-treatment safety impact (up to W96) notably on the neurodevelopment of the children.
- All target IHs improved as soon as D7 (8/11) or ≤W4. Complete resolution was reported in 4 cases, all on or after treatment with the 3 mg/kg/day dosage, 3 of which were sustained up to W96/EOS.
3. *Final report of the Compassionate Use Program*
### COMPASSIONATE USE PROGRAM (CUP)
#### FINAL BRIDGING REPORT FOR:

<table>
<thead>
<tr>
<th>PROPRANOLOL</th>
<th>PIERRE FABRE DERMATOLOGIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral solution</td>
<td>(3.75 mg/ml propranolol)</td>
</tr>
</tbody>
</table>

**EXPLOITANT NAME**
PIERRE FABRE DERMATOLOGIE

**and CONTACT DETAILS**
45, place Abel-Gance
92 100 BOULOGNE
France

**Period covered:**
13-APR-2010 / 31-JUL-2014

**Date of the first ATU (France):**
13 -APR - 2010

**Author:**
Emel BELKEBIR, PharmD,
Corporate Drug Safety Officer Associate
Geneviève LEBBÉ, PharmD,
Corporate Drug Safety Officer

**Head of Corporate Vigilances Division:**
Emmanuelle PINÈS, MD

**Document Type:**
Final CUP Bridging report

**Date of this report (final version):**
05/12/2014

**Number of pages:**
58

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EXECUTIVE SUMMARY

This third and final bridging report for the compassionate use programme (CUP) of Propranolol Pierre Fabre Dermatologie (oral solution, 3.75 mg/ml Propranolol) was written by Pierre Fabre Corporate Vigilances Division (CVD). This report covers the entire period of compassionate use programme from 13th April 2010 to 31st July 2014.

The “nominative” CUP for Propranolol Pierre Fabre Dermatologie was initiated in France on 13th April 2010. On 30-May-2012, The French health agency (ANSM) gave its agreement to switch from a “nominative” (named patient program) to a “cohort” CUP which started on 13th July 2012 and ended on 31st July 2014.

Propranolol Pierre Fabre Dermatologie was given in this program to infants with proliferating infantile haemangioma which are life-threatening or give rise to a functional risk, and ulcerative hemangiomas not responding to simple treatment and who could not be included in the ongoing clinical studies (V0400SB: Project code used in clinical trials for Propranolol).

This report includes a descriptive analysis of all cumulative data in the context of the protocol for therapeutic use and information collection, as well as any new relevant information on the medicinal product gathered since the cohort CUP was granted.

Cumulatively, 1661 patients have been treated in the frame of the CUP. Overall 161 cases have reported a total of 259 adverse drug reactions (ADRs), including 40 serious cases with 61 serious ADRs. Three (3) of these cases were fatal, but the event leading to fatal outcome was considered to be:
- doubtfully related to Propranolol in one case (FR-2011-1487: serious AV block complete and acute cardiac failure),
- not related in the second case (FR-2014-1013: choking on food and asthma) and
- not assessable in the third case (FR-2014-1442: drug ineffective and off-label use)

The most frequently reported ADRs were bronchiolitis (38 ADRs, of which 12 serious) and sleep disorders such as nightmares and insomnia (39 ADRs, all non-serious).
The following four (4) categories of serious ADRs have been considered as important identified risks for this population and are mentioned as such in the approved risk management plan for Hemangiol®, trade name of the medicinal product for which the marketing authorisation was granted since then in the European economic area:

- **Cardiac disorders**: bradycardia and prolonged atrio-ventricular conduction or intensification of an AV block
- **Vascular disorders**: hypotension
- **Respiratory disorders**: bronchospasm and bronchial hyperreactivity reactions
- **Metabolism and nutritional disorders**: hypoglycaemia and related seizures

In addition, since March 2011, a CUP was initiated in Switzerland. There is no defined protocol for therapeutic use or information collection defined in the frame of this CUP. As of 31st July 2014, a total of 105 patients have been treated with Propranolol Pierre Fabre Dermatologie 3.75 mg/mL in the Swiss CUP. Pierre Fabre has received no ADRs from the SwissMedic agency.

The first MA for Propranolol was obtained on 14th March 2013 through national procedure in the United States of America (USA) under the trade name of Hemangeol®. The product was also registered through centralised procedure in Europe under the trade name of Hemangiol®; the MA was obtained on 23rd April 2014.

The therapeutic information for prescribers dated November 2009 was the Reference Safety Information in effect at the beginning of the reporting interval. The therapeutic information for prescribers dated July 2012 was the Reference Safety Information in effect at the data lock point of this report.

The safety profile of Propranolol Pierre Fabre Dermatologie administered in infants with proliferating infantile hemangiomas requiring systemic therapy in the context of the French CUP remains favourable and no modification of the reference safety document in use at the end of this report was deemed necessary.

The safety information retrieved from the CUP has been implemented in the European SPC and in the United State prescribing information. The company core data sheet, released in December 2014, has become the reference safety information for Hemangiol®/Hemangeol®.
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ABBREVIATIONS

ADR: Adverse Drug Reaction
ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé
CUP: Compassionate Use Program
ECG: Electrocardiogram
HCP: Health Care Professional
MA: Marketing Authorisation
MAH: Marketing Authorisation Holder
MedDRA: Medical Dictionary for Regulatory Activities
PF: Pierre Fabre
PF CVD: Pierre Fabre Corporate Vigilances Division
PFD: Pierre Fabre Dermatologie
PSUR: Periodic Safety Update Report
PT: Preferred Term
PUT: Protocole d’Utilisation Thérapeutique et de recueil d’information (Protocol for therapeutic use)
SOC: System Organ Class
SPC: Summary of Product Characteristics (replaced by the Therapeutic Information for Prescribers in the PUT)
SUSAR: Suspected Unlisted Serious Adverse Reaction
1 DATA COLLECTED IN THE CONTEXT OF A TEMPORARY AUTHORISATION FOR USE SUBJECT TO A PROTOCOL FOR USE AND INFORMATION COLLECTION

This is the third bridging compassionate use programme report for Propranolol prepared by Pierre Fabre Corporate Vigilances Division. The safety experience of this compassionate use programme was reviewed in 2 previous bridging reports.

This report covers the entire period of compassionate use programme from 13th April 2010 to 31st July 2014. However, data are presented in this report highlighting both cumulative period and data available since the last compassionate use programme report:
- The period covering 13th October 2013 to 31st July 2014,
- The cumulative period since the first authorisation on 13th April 2010 to 31st July 2014.

A nominative “CUP” (compassionate use programme) for Propranolol Pierre Fabre Dermatologie was initiated in France on 13th April 2010. On 30 May 2012, The French health agency (ANSM) gave its agreement to switch from a nominative (named patient program) to a cohort CUP which started on 13th July 2012 and ended on 31st July 2014. No differentiation was made on the data presented hereafter, between these 2 types of ATU (except for Table 1).

1.1 POPULATION

The indication of this compassionate use programme is the treatment of proliferating infantile hemangiomas which are life-threatening or give rise to a functional risk, and ulcerative hemangiomas not responding to simple treatment, in infants unable to be included in a clinical trial (V0400SB: Project code used in clinical trials for Propranolol).
1.1.1. NUMBER OF PATIENTS INCLUDED IN THE CUP PROGRAM

A total of 1661 patients have been included in the program since the first authorisation.

Table 1: Number of patients included in the ATU program

<table>
<thead>
<tr>
<th>Since the last compassionate use programme</th>
<th>Number of patients included since the first authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=500</td>
<td>N=1661</td>
</tr>
<tr>
<td>Initiated in ‘nominative ATU’ N=0</td>
<td>Initiated in ‘cohort ATU’ N=500</td>
</tr>
<tr>
<td>D1 form N=0</td>
<td>D1 form N=500</td>
</tr>
</tbody>
</table>

| Initiated in ‘nominative ATU’ N=573        | Initiated in ‘cohort ATU’ N=1088                         |
| D1 form N=557                             | D1 form N=1088                                          |

Number of D1 forms available for analysis

N=500

Number of D1 forms available for analysis

N=1645

Note: D1 form corresponds to patients for whom the application form for access to the program was received.

Cumulatively, 9 temporary authorisation requests have not been approved. The majority of these requests were refused because of the absence of haemangioma or only presence of an aesthetic impairment, or because of the inappropriate age of the patient. One of these patients was refused in “cohort” program but was accepted in the “nominative” compassionate use program for Pompe disease, by derogation.

For the following sections (until 1.3.3.1), available data are only based on patients for whom the application form for access to the program (D1 form) was received.

Cumulatively, since some documents have not been received by the company despite reminders, D1 form is available for 1645 patients among the 1661 patients included since the first authorisation.

All application forms for treatment initiated since the start of the cohort are available.

D1 form is available for all the 500 new patients included during the reference period.

Therefore, the initial characteristics of patients and geographic distribution are described for 500 patients during the reference period and for 1645 patients cumulatively.
1.1.2. GENDER OF PATIENTS

Table 2: Gender of patients

<table>
<thead>
<tr>
<th>Gender (n%)</th>
<th>Since the last compassionate use programme report (N=500)</th>
<th>Since the first authorisation (13/APR/2010) (N=1645)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>489</td>
<td>1628</td>
</tr>
<tr>
<td>Female</td>
<td>371 (75.9%)</td>
<td>1227 (75.4%)</td>
</tr>
<tr>
<td>Male</td>
<td>118 (24.1%)</td>
<td>401 (24.6%)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

1.1.3. AGE OF PATIENTS

Table 3: Age of patients at inclusion

<table>
<thead>
<tr>
<th>Age</th>
<th>Since the last compassionate use programme report (N=500)</th>
<th>Since the first authorisation (13/APR/2010) (N=1645)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>500</td>
<td>1645</td>
</tr>
<tr>
<td>Minimal</td>
<td>3 days</td>
<td>1 days</td>
</tr>
<tr>
<td>Maximal</td>
<td>1650 days (4.5 years)</td>
<td>2354 (6.4 years)</td>
</tr>
<tr>
<td>Average</td>
<td>158.2 days (5.2 months)</td>
<td>171.0 days (5.6 months)</td>
</tr>
<tr>
<td>Median</td>
<td>112 days (3.7 months)</td>
<td>115 days (3.8 months)</td>
</tr>
</tbody>
</table>

The figures 1 and 2 show the distribution by age.
Figure 1: Age of patients at inclusion, during the period covered by this report (N=500)

![Age of patients at inclusion](image)

Figure 2: Cumulative data on the age of patients at inclusion (N=1645).

**PAST MEDICAL HISTORY OF INCLUDED PATIENTS**

Table 4: Birth weight

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Since the last compassionate use programme report N=500</th>
<th>Since the first authorisation (13/APR/2010) N=1645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>454</td>
<td>1501</td>
</tr>
<tr>
<td>Minimal</td>
<td>0.62 kg</td>
<td>0.52 kg</td>
</tr>
<tr>
<td>Maximal</td>
<td>4.5 kg</td>
<td>4.88 kg</td>
</tr>
<tr>
<td>Average</td>
<td>3.01 kg</td>
<td>2.98 kg</td>
</tr>
</tbody>
</table>
Table 5: Prematurity state

<table>
<thead>
<tr>
<th>Premature patients</th>
<th>Since the last compassionate use programme report N=500</th>
<th>Since the first authorisation (13/APR/2010) N=1645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature patients</td>
<td>115/493 (23.3 %)</td>
<td>374/1635 (22.9 %)</td>
</tr>
<tr>
<td>Corrected age reached for premature patients</td>
<td>105/108 (97.2%)</td>
<td>356/365 (97.5 %)</td>
</tr>
</tbody>
</table>

Cumulatively, nine (9) premature born patients, who had not reached their corrected age, started the treatment. Six (6) patients were included in the “cohort” ATU program and 3 patients were included in the “nominative” ATU program.

Table 6: Medical history (no distinction between past and current)

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Since the last compassionate use programme report N=500</th>
<th>Since the first authorisation (13/APR/2010) N=1645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac diseases</td>
<td>16/499 (3.2 %)</td>
<td>44/1642 (2.7 %)</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1/498 (0.2%)</td>
<td>2/1641 (0.1 %)</td>
</tr>
<tr>
<td>Asthma</td>
<td>2/485 (0.4%)</td>
<td>7/1624 (0.4 %)</td>
</tr>
<tr>
<td>Bronchitis/bronchiolitis</td>
<td>32/486 (6.6%)</td>
<td>68/1418 (4.8 %)</td>
</tr>
<tr>
<td>Atopic state</td>
<td>111/477 (23.3%)</td>
<td>306/1599 (19.1 %)</td>
</tr>
<tr>
<td>Other pathology</td>
<td>22/454 (4.8%)</td>
<td>78/1369 (5.7 %)</td>
</tr>
</tbody>
</table>

n/number of available data (%)
1.1.4. GEOGRAPHICAL DISTRIBUTION OF PATIENTS

The geographical distribution of the patients was presented according to French administrative regions. It was considered that the patient’s parents consulted the hospital physicians of their regions. During the period covered by this report, the first region of inclusion was *Ile de France*, followed by *Nord-Pas-de-Calais* then *Pays de la Loire*.

Considering cumulative data since the beginning of the ATU, the first region of inclusion was *Ile de France*, followed by *Nord-Pas-de-Calais* then *Aquitaine* (figure 3).

![Geographical distribution of patients](image)

**Figure 3:** Geographical distribution of patients since the beginning of the ATU (N=1645)
1.1.5. PRESCRIBERS POPULATION

Since the first authorisation, a total of 330* physicians have prescribed chlorhydrate de propranolol Pierre Fabre Dermatologie including:

- 186 (56.3%) pediatricians (pediatrician, neonatalogist, surgoenpediatrician, pneumopediatrician, gastropediatrician, neuropediatrician, oncopediatrician)
- 113 (34.2 %) dermatopediatricians and dermatologists
- 22 (6.7%) cardiopediatricians and cardiologists
- 9 (2.7%) other (ENT, hospital general practitioner)

Among these prescribers, 51 worked in hospitals of Ile de France (15.5%), 34 in Bretagne (10.3%) and 32 in Rhône-Alpes (9.7%). The number of prescribers was large but the majority has recruited few patients. The most recruiting hospitals were the following university hospitals: Necker Hospital in Paris (267 patients), Lille (158 patients), Bordeaux (135 patients) and Toulouse (81 patients).

* Of note, these data are based on the D1 forms filled by physicians.

1.2. PROLIFERATIVE INFANTILE HEMANGIOMA

1.2.1. LOCALISATION AND SIZE

Table 7: Localisation and size of infantile haemangioma

<table>
<thead>
<tr>
<th>Localisation and size</th>
<th>Since the last compassionate use programme report</th>
<th>Since the first authorisation (13/APR/2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=500</td>
<td>N=1645</td>
</tr>
<tr>
<td>Haemangioma localized on the face</td>
<td>307/500 (61.4 %)</td>
<td>1031/1645 (62.7 %)</td>
</tr>
<tr>
<td>with largest diameter &gt; 1.5 cm</td>
<td>245/279 (87.8 %)</td>
<td>819/951 (86.1 %)</td>
</tr>
<tr>
<td>Haemangioma localized on the body</td>
<td>213/500 (42.6 %)</td>
<td>692/1645 (42.1 %)</td>
</tr>
<tr>
<td>Haemangioma with internal localisation</td>
<td>45/497 (9.1 %)</td>
<td>151/1619 (9.3 %)</td>
</tr>
<tr>
<td>Multiple hemangioma (&gt;= 3)</td>
<td>37/500 (7.4 %)</td>
<td>142/1645 (8.6 %)</td>
</tr>
</tbody>
</table>

Of note, this table is based on data provided by D1 forms. As the physician had the possibility to tick multiple boxes per patient, the sum of percentages is over 100%.
### 1.2.2. SEVERITY

Table 8: Severity of infantile haemangioma

<table>
<thead>
<tr>
<th>Severity</th>
<th>Since the last compassionate use programme report (N=500)</th>
<th>Since the first authorisation (13/APR/2010) (N=1645)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional impairment</td>
<td>354/497 (71.2 %)</td>
<td>1166/1610 (72.4 %)</td>
</tr>
<tr>
<td>Severe ulceration</td>
<td>184/482 (38.2 %)</td>
<td>624/1587 (39.3 %)</td>
</tr>
<tr>
<td>Vital risk</td>
<td>74/488 (15.2 %)</td>
<td>249/1579 (15.8 %)</td>
</tr>
</tbody>
</table>

Of note, this table is based on data provided by D1 forms. As the physician had the possibility to tick multiple boxes per patient, the sum of percentages is over 100%.
## 1.3. TREATMENTS

### 1.3.1. PREVIOUS TREATMENTS FOR HAEMANGIOMA

Table 9: Previous treatment for infantile hemangioma

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th>Since the last compassionate use programme report</th>
<th>Since the first authorisation (13/APR/2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>481</td>
<td>1606</td>
</tr>
<tr>
<td>No previous treatment</td>
<td>421 (87.5%)</td>
<td>1342 (83.6%)</td>
</tr>
<tr>
<td>Propranolol or beta-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol or other beta-blockers alone</td>
<td>22 (4.6%)</td>
<td>97 (6.0 %)</td>
</tr>
<tr>
<td>Propranolol and systemic corticoids</td>
<td>-</td>
<td>3 (0.2 %)</td>
</tr>
<tr>
<td>Propranolol and Vincristine</td>
<td>-</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Propranolol and other beta-blocker, both by unspecified route.</td>
<td>1(0.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Propranolol and other local beta-blocker.</td>
<td>-</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Beta-blocker and systemic corticotherapy</td>
<td>-</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>Beta-blocker, systemic corticotherapy, vincristine</td>
<td>-</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>Propranolol or beta-blockers associated with other treatments</td>
<td>2 (0.4%)</td>
<td>10 (0.6 %)</td>
</tr>
<tr>
<td>Systemic therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic corticoids</td>
<td>2 (0.4%)</td>
<td>19 (1.2%)</td>
</tr>
<tr>
<td>Systemic corticoids and vincristine</td>
<td>-</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Systemic corticoids and Local corticoids</td>
<td>-</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>Systemic corticoids and other treatment</td>
<td>2 (0.4%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Local treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local corticoids</td>
<td>-</td>
<td>9 (0.6%)</td>
</tr>
<tr>
<td>Local corticoids and other treatments</td>
<td>-</td>
<td>3 (0.2 %)</td>
</tr>
<tr>
<td>Other* / Unspecified previous treatment</td>
<td>31 (6.4%)</td>
<td>112 (7.0 %)</td>
</tr>
<tr>
<td>Surgery</td>
<td>-</td>
<td>1 (0.1 %)</td>
</tr>
</tbody>
</table>

*Other treatments were principally local cares, such as dressings, Peru balsam, hydrocolloids, disinfectants, local treatment (fucidin) and laser.
1.3.2. CONCOMITANT MEDICINAL PRODUCTS

The concomitant medicinal products at initiation of treatment with Chlorhydrate de Propranolol Pierre Fabre Dermatologie included the usual vitamin, iron and fluorides supplements for infants.

Of note, more than 80% of patients did not have any concomitant treatments.

Table 10: Concomitant treatments reported at treatment initiation

<table>
<thead>
<tr>
<th>Concomitant medicinal products</th>
<th>Since the last compassionate use programme report N=500</th>
<th>Since the first authorisation (13/APR/2010) N=1645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>500</td>
<td>1645</td>
</tr>
<tr>
<td>No concomitant treatment</td>
<td>438 (87.6%)</td>
<td>1415 (86.0%)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>5 (1.0%)</td>
<td>24 (1.5%)</td>
</tr>
<tr>
<td>Vitamin D or fluorides</td>
<td>34 (6.8%)</td>
<td>139 (8.4%)</td>
</tr>
<tr>
<td>Other treatments*</td>
<td>20 (4.0%)</td>
<td>70 (4.3%)</td>
</tr>
<tr>
<td>Iron</td>
<td>10 (2.0%)</td>
<td>39 (2.4%)</td>
</tr>
<tr>
<td>Systemic Corticoids</td>
<td>11 (2.2%)</td>
<td>32 (1.9%)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>5 (1.0%)</td>
<td>32 (1.9%)</td>
</tr>
<tr>
<td>Proton Pomp Inhibitor</td>
<td>13 (2.6%)</td>
<td>30 (1.8%)</td>
</tr>
<tr>
<td>Vitamin B</td>
<td>3 (0.6%)</td>
<td>13 (0.8%)</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td>2 (0.4%)</td>
<td>7 (0.4%)</td>
</tr>
<tr>
<td>Local antibiotics</td>
<td>1 (0.2%)</td>
<td>7 (0.4%)</td>
</tr>
<tr>
<td>Local Corticoids</td>
<td>2 (0.4%)</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Biliary acids</td>
<td>-</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1 (0.2%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Local Beta Blocker</td>
<td>-</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

n(%)  
*Others treatments included: analgesic/antipyretics (paracetamol, ibuprofen), antireflux/anticacids (domperidone, omeprazole, sodium alginate), anti infectious drugs (josamycin, fucidine, miconazole, amphotericin b), vitamin/folic acid, aldactone, levothyrox, ventolin and adrenalin aerosol.
1.3.3. CHLORHYDRATE DE PROPRANOLOL PIERRE FABRE DERMATOLOGIE, ORAL SOLUTION

Weight at treatment demand, posology, duration and discontinuation are described hereafter only on the population since the first authorisation (13th April 2010).

1.3.3.1. Weight at treatment demand

Table 11: Weight at treatment demand

<table>
<thead>
<tr>
<th>Weight at treatment demand</th>
<th>Since the first authorisation (13/APR/2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>1621</td>
</tr>
<tr>
<td>Minimal</td>
<td>1.9 kg</td>
</tr>
<tr>
<td>Maximal</td>
<td>29.0 kg</td>
</tr>
<tr>
<td>Average</td>
<td>6.3 kg</td>
</tr>
<tr>
<td>Median</td>
<td>5.9 kg</td>
</tr>
</tbody>
</table>

1.3.3.2. Posology

The mean treatment posology was 2.0 mg/kg/day of propranolol oral solution with minimum of 0.4 mg/kg/day and maximum of 4 mg/kg/day. The median was 2.0 mg/kg/day. This table is based on the initial planned treatment posology by the physician on D1 form.

Table 12: Treatment posology

<table>
<thead>
<tr>
<th>Planned daily dose at initial demand</th>
<th>Since the last compassionate use programme report N=500</th>
<th>Since the first authorisation (13/APR/2010) N=1645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>469</td>
<td>1587</td>
</tr>
<tr>
<td>Minimal</td>
<td>0.5 mg/kg/day</td>
<td>0.4 mg/kg/day</td>
</tr>
<tr>
<td>Maximal</td>
<td>3.6 mg/kg/day</td>
<td>4.0 mg/kg/day*</td>
</tr>
<tr>
<td>Average</td>
<td>2.0 mg/kg/day</td>
<td>2.0 mg/kg/day</td>
</tr>
<tr>
<td>Median</td>
<td>2.0 mg/kg/day</td>
<td>2.0 mg/kg/day</td>
</tr>
</tbody>
</table>

* Of note, one patient with axillar haemangioma (5x7 cm) with hemorrhagic risk, was planned to start treatment at a dose of 2 mg/kg/12h (i.e. 4 mg/kg/day). Treatment was renewed after 3 months, at a dose of 2 mg/kg/day. After 7 months of treatment, the patient discontinued due to insufficient efficacy.
At the beginning of the ATU, only the planned daily dose was registered with possible confounding interpretation between the initial and titration dose. Since the beginning of the cohort ATU, the posology administered after the titration phase was registered.

This data for initiation daily dose is available on only 1217 patients (cumulatively) and is similar: mean value of 2.0 mg/kg/day and median value of 2.0 mg/kg/day.

1.3.3.3. Treatment duration

Methodology for estimation

At the beginning of the ATU, the treatment end date had not been requested on the forms. It is requested since the beginning of the cohort ATU.

Therefore, treatment duration was calculated considering the date of signature of discontinuation form D5* [signature date of the treatment discontinuation form – first intake of treatment date+1]. However, when available, the date of discontinuation was considered.

* When D5 form was not available, information provided in D3 form was considered.

Results

The estimated mean treatment duration was 262.7 days (8.6 months), with minimum of 3 days and maximum of 1119 days. The median was 221 days (7.3 months).

Table 13: Estimated treatment duration

<table>
<thead>
<tr>
<th>Treatment duration based on date of signature of D5 form</th>
<th>Since the first authorisation (13/APR/2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>657 / 699</td>
</tr>
<tr>
<td>Minimal</td>
<td>3 days</td>
</tr>
<tr>
<td>Maximal</td>
<td>1119 days (36.8 months)</td>
</tr>
<tr>
<td>Average</td>
<td>262.7 days (8.6 months)</td>
</tr>
<tr>
<td>Median</td>
<td>221 days (7.3 months)</td>
</tr>
</tbody>
</table>
1.3.3.4. Treatment discontinuation

Reasons of treatment discontinuation are reported on the discontinuation form D5.

Table 14: Treatment discontinuation

<table>
<thead>
<tr>
<th>Reasons for treatment discontinuation</th>
<th>Since the first authorisation (13/APR/2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of available data</td>
<td>697*</td>
</tr>
<tr>
<td>AE</td>
<td>29 (4.2%)</td>
</tr>
<tr>
<td>Good efficacy</td>
<td>584 (83.8%)</td>
</tr>
<tr>
<td>Insufficient efficacy</td>
<td>28 (4.0%)</td>
</tr>
<tr>
<td>Onset of an unspecified contraindication</td>
<td>20 (2.9%)</td>
</tr>
<tr>
<td>Unknown other reason (detail not collected)</td>
<td>45 (6.5%)</td>
</tr>
</tbody>
</table>

* Of note, 2 patients were lost to follow up.

A table presenting treatment discontinuations due to an adverse event is provided in section 2.1.1.2. Definitive treatment discontinuation for an adverse event.

1.3.3.5. Efficacy data

It had not been planned in the “nominative” compassionate use programme to register details concerning the efficacy of Chlorhydrate de Propranolol Pierre Fabre Dermatologie. Data on treatment efficacy is based on the information provided on the D5 forms of the protocol for therapeutic use. On D5 forms, physicians report the reason for treatment discontinuation. Reasons for treatment discontinuation are provided in table 1.3.3.4. In order to evaluate efficacy data, “treatment discontinuations for good efficacy” and “treatment discontinuations for insufficient efficacy” are analysed.

Based on the information provided on the available D5 forms for 697 patients, treatment was considered by the physicians as:

- sufficiently efficient for 584 patients (83.8%).
- insufficiently efficient for 28 patients (4.0%).

Since the beginning of the “cohort” compassionate use programme, treatment efficacy is also evaluated by physicians during treatment, by completing D3 forms of the protocol, providing the following results. Of note, these results are of limited relevance due to the small number of forms completed:
Concerning the period of 2 to 3 months after the first treatment intake, forms were received for 210/1088 (19.3%) patients.

Among these 210 patients, the haemangioma had decreased in 176 (83.8%) patients and 4 patients (1.9%) had completely recovered.

Concerning the period of 5 to 6 months after the first treatment intake, forms were received for 123/1088 (11.3%) patients. Among these 123 patients, the haemangioma had decreased in 86 patients (69.9%) and 10 patients (8.1%) had completely recovered.

2. PHARMACOVIGILANCE DATA IN FRANCE

Since 13-Apr-2010, among the 1661 patients included in the compassionate use program, 161 patients (9.7%) have experienced at least one ADR, for a total of 259 ADRs.

Table 15: Summary of data since the first CUP

<table>
<thead>
<tr>
<th>Total number of included patients</th>
<th>Total number of cases</th>
<th>Total number of serious cases</th>
<th>Total number of ADR</th>
<th>Total number of serious ADR</th>
<th>Total number of fatal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1661</td>
<td>161</td>
<td>40</td>
<td>259</td>
<td>61</td>
<td>3</td>
</tr>
</tbody>
</table>

Three (3) cases with a fatal outcome have been reported:

- FR-2011-1487: One case of atrioventricular block complete and acute cardiac failure was considered as doubtfully related to the treatment considering the cardiac safety monitoring since the introduction of Propranolol, the underlying diseases, the numerous concomitantly taken medicines and therapeutic endoscopic procedure. This case is described in section 2.3.

- FR-2014-1442: One case of drug ineffective concerned a 03-day-old patient, which is considered as an off label use. According to the physician, the patient died in a context of lack of efficacy of the product in a context of complication of the initial diagnosis with major cerebral lesions. The final diagnosis was multifocal lymphangioendotheliomatosis. The causal relationship was not assessable for drug ineffective and off label use.

- FR-2014-1013: A 12-month-old female patient died due to choking on food. The causal relationship between Propranolol and death due to choking on food was assessed as not related by the physician and the company because the patient had discontinued the treatment with Propranolol since at least 2 months.

The analysis of these cases did not allow identifying a new safety signal.
2.1. ADVERSE DRUG REACTIONS BY SYSTEM ORGAN CLASS AND PREFERRED TERM

All ADRs reported since the beginning of the CUP, are presented in the table hereafter by System Organ Class according to MedDRA version 17.1.

Of note, seriousness assessment of each case is based on the primary ADR, e.g. main ADR/Diagnosis of each case. The SOC assigned to each case corresponds to that of the primary ADR.

The SOCs in which ADRs were most frequently reported were “Infections and infestations”, with 55 ADRs (15 were serious), followed by the SOC “Psychiatric disorders” with 51 ADRs (all non-serious).

In addition, a significant proportion of the reported ADRs were considered as serious for the following SOCs: “Cardiac disorders” (6/7 ADRs), “Respiratory, thoracic, and mediastinal disorders” (12/21 ADRs) and “Nervous system disorders” (6/14 ADRs).

A summary of non-serious and serious ADRs is presented by SOC and preferred term (PT) in Table 16.

The most frequently reported ADRs were:
- Bronchiolitis (38 ADRs including 12 serious), which is a common childhood event for which the causal relationship with Propranolol is difficult to establish.
- Sleep disorders such as insomnia and nightmare (39 non-serious ADRs),
- Agitation (8 non-serious ADRs),
- Decreased appetite (8 including 1 serious ADRs)
- Hypoglycaemia (8 including 5 serious ADRs)
Table 16: ADRs and Serious ADRs by System Organ Class (SOC) and Preferred Term (PT)

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS (MedDRA V17.0)</th>
<th>Cases</th>
<th>Adverse Drug Reactions (ADR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Fatal cases</td>
<td>Number of cases* (serious)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3</td>
<td>161 (40)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>1</td>
<td>4 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear, Labyrinth disorders</td>
<td>0</td>
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<td>SYSTEM ORGAN CLASS (MedDRA V17.0)</td>
<td>Cases</td>
<td>Adverse Drug Reactions (ADR)</td>
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<td>Number of cases* (serious)</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Skin and subcutaneous tissue disorders</td>
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</tr>
</tbody>
</table>

Source: Cumulative Summary Tabulation of events and Line listing of cases covering 13.04.2010 to 31.07.2014

* cases for which the Preferred Term is the main event.

Note: One patient can be involved in several cases, each composed of one or more ADRs. Each case has a main ADR/ diagnosis. The SOC assigned to a case corresponds to the main ADR of that case. Similarly the seriousness of a case corresponds to the seriousness of the main ADR of that case.
2.2. ADVERSE DRUG REACTIONS LEADING TO CHANGE IN DOSE OR DISCONTINUATION OF TREATMENT

The dose of Propranolol oral solution 3.75 mg/mL was reduced in 19 patients with ADRs, including one serious case of bronchospasm, one serious case of condition aggravation and one serious case of malaise.

The dose of Propranolol oral solution 3.75 mg/mL was temporarily discontinued due to ADRs in 30 patients, including six serious cases (hypotension, bronchiolitis (2), purpura, bradycardia, hypotonia and malaise and respiratory syncytial virus bronchiolitis).

The dose of Propranolol oral solution 3.75 mg/mL was definitely discontinued due to ADRs in 43 patients, among them 17 ADRs were serious:

- One case of complete AV block and fatal heart failure
- One case of bradycardia and sinus arrest
- One case of bradycardia, hypotonia and malaise
- Ten (10) cases of severe or recurrent bronchiolitis
- Three (3) cases or severe hypoglycaemia (one with asthenia, somnolence; one with hypoglycaemic seizure, bradycardia, medication error and one case with intentional drug misuse).
- One case of asthma.
Table 17: ADRs Leading to Change in Dose or Discontinuation of Treatment

<table>
<thead>
<tr>
<th>Propranolol oral solution 3.75 mg/mL action due to Event (Case number)</th>
<th>ADRs leading to treatment dose change/ discontinuation</th>
<th>Serious</th>
<th>Causality as determined by the company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose decreased</strong></td>
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</tr>
<tr>
<td>FR-2010-2876</td>
<td>Erythema Vasoconstriction</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2011-1903</td>
<td>Initial insomnia Sleep disorder</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>FR-2012-0075</td>
<td>Agitation Abnormal behaviour Decreased appetite</td>
<td>No</td>
<td>Doubtful</td>
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<tr>
<td>FR-2011-0326</td>
<td>Bronchospasm</td>
<td>Yes</td>
<td>Doubtful</td>
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<tr>
<td>FR-2013-2949</td>
<td>Crying</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2013-1311</td>
<td>Condition aggravated</td>
<td>Yes</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2013-0457</td>
<td>Nightmare</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>FR-2013-2204</td>
<td>Hypoglycaemia Pallor Hyperhidrosis Somnolence</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>FR-2013-2055</td>
<td>Middle insomnia</td>
<td>No</td>
<td>Possible</td>
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<tr>
<td>FR-2013-2171</td>
<td>Nightmare</td>
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<td>Doubtful</td>
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<tr>
<td>FR-2013-1098</td>
<td>Middle insomnia Nightmares</td>
<td>No</td>
<td>Possible</td>
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<tr>
<td>FR-2013-2862</td>
<td>Raynaud’s syndrome Peripheral coldness Oedema peripheral</td>
<td>No</td>
<td>Possible</td>
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<tr>
<td>FR-2013-1933</td>
<td>Pallor Hypotonia Decreased appetite</td>
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<td>Possible</td>
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<td>FR-2014-0691</td>
<td>Vomiting Hypotension Pallor Hypotonia</td>
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<tr>
<td>FR-2014-2462</td>
<td>Diarrhoea Vomiting</td>
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<td>FR-2014-0817</td>
<td>Malaise Peripheral coldness</td>
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<tr>
<td>FR-2014-1312</td>
<td>Abnormal weight gain Nightmare Inappropriate schedule of drug administration</td>
<td>No</td>
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<td>FR-2014-0184</td>
<td>Sleep disorders</td>
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<td>Cough</td>
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<td>Unknown (not assessable)</td>
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<td><strong>Temporarily Discontinued</strong></td>
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<tr>
<td>FR-2011-0782</td>
<td>Somnolence</td>
<td>No</td>
<td>Doubtful</td>
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<tr>
<td>FR-2012-1543</td>
<td>Bronchiolitis</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2012-1752</td>
<td>Diarrhea Abdominal pain Flatusulence</td>
<td>No</td>
<td>Probable</td>
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### Propranolol oral solution 3.75 mg/mL action due to Event

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<tr>
<th>Case number</th>
<th>ADRs leading to treatment dose change/ discontinuation</th>
<th>Serious</th>
<th>Causality as determined by the company</th>
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<tbody>
<tr>
<td>FR-2011-0777</td>
<td>Bronchiolitis Incorrect dose administered</td>
<td>Yes</td>
<td>Doubtful Unknown (Not assessable)</td>
</tr>
<tr>
<td>FR-2011-1422</td>
<td>Bronchiolitis (3 episodes)</td>
<td>Yes</td>
<td>Probable</td>
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<tr>
<td>FR-2011-0662</td>
<td>Purpura</td>
<td>Yes</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2011-0698</td>
<td>Hypotension</td>
<td>Yes</td>
<td>Possible</td>
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<tr>
<td>FR-2012-1919</td>
<td>Bronchitis Nasopharyngitis</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2012-2232</td>
<td>Abnormal behaviour Sleep disorder Peripheral vasoconstriction</td>
<td>No</td>
<td>Possible</td>
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<td>FR-2012-4019</td>
<td>Bronchiolitis</td>
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<td>FR-2012-4027</td>
<td>Bronchiolitis</td>
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<td>Doubtful</td>
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<tr>
<td>FR-2012-3688</td>
<td>Bradycardia, Hypotonia, Malaise</td>
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<td>FR-2013-1070</td>
<td>Constipation</td>
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<td>FR-2013-2088</td>
<td>Sleep disorders Failure to thrive Weight gain poor</td>
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<td>FR-2014-0906</td>
<td>Regurgitation Hypophagia</td>
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<td>FR-2014-1118</td>
<td>Respiratory syncytial virus bronchiolitis</td>
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<td>Hypoglycaemia</td>
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<td>Possible</td>
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<td>FR-2014-1621</td>
<td>Failure to thrive Decreased appetite</td>
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### Permanently discontinued

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<td>FR-2011-0464</td>
<td>Bradycardia Sinus arrest</td>
<td>Yes</td>
<td>Possible</td>
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<tr>
<td>FR-2010-2869</td>
<td>Bronchiolitis (2 episodes: 1 temp. disc., 1 perm. disc.)</td>
<td>Yes</td>
<td>Probable</td>
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<tr>
<td>FR-2011-0643</td>
<td>Bronchiolitis</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>FR-2011-1570</td>
<td>Bronchiolitis (3 episodes: 2 temp. disc. 1 perm. disc.)</td>
<td>No</td>
<td>Possible</td>
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<td>Propranolol oral solution 3.75 mg/mL action due to Event (Case number)</td>
<td>ADRs leading to treatment dose change/ discontinuation</td>
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<td>Hypoglycaemia</td>
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<td>Asthenia</td>
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<td>Somnolence</td>
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<td>Middle insomnia</td>
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<td>Nightmares</td>
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<td>FR-2011-0467</td>
<td>Respiratory arrest</td>
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<td>Shock</td>
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<td>Bronchiolitis</td>
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<td>FR-2011-0752</td>
<td>Bronchospasm</td>
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<td>Bronchiolitis</td>
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<td>FR-2011-1487*</td>
<td>Complete AV block</td>
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<td>Fatal acute cardiac failure</td>
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<td>FR-2012-3510</td>
<td>Diarrhea</td>
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<td>FR-2012-2108</td>
<td>Chills</td>
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<td>Agitation</td>
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<td>Hypoglycaemic seizure</td>
<td>Yes</td>
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</tr>
<tr>
<td></td>
<td>Bradycardia</td>
<td>Yes</td>
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</tr>
<tr>
<td></td>
<td>Medication error</td>
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</tr>
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<td>FR-2012-4138</td>
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<td>FR-2012-4019</td>
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<td>FR-2013-1358</td>
<td>Purpura</td>
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</tr>
<tr>
<td>FR-2012-3969</td>
<td>Malaise, hypotonia, vomiting, anorexia</td>
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</tr>
<tr>
<td>FR-2013-1359</td>
<td>Bronchiolitis</td>
<td>No</td>
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<td>FR-2013-1745</td>
<td>Bronchiolitis</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td>FR-2013-1219</td>
<td>Failure to thrive</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
<td></td>
<td>Weight stagnation</td>
<td>No</td>
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<td>FR-2013-0259</td>
<td>Respiratory distress</td>
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<td>Bronchiolitis</td>
<td>Yes</td>
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<tr>
<td>FR-2013-1654</td>
<td>Cough</td>
<td>No</td>
<td>Doubtful</td>
</tr>
<tr>
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<td>Sleep disorders</td>
<td>No</td>
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<td>FR-2013-1987</td>
<td>Bronchospasm</td>
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<td>FR-2013-1986</td>
<td>Bronchospasm</td>
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<td>FR-2013-2137</td>
<td>Cough</td>
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<td>Sleep disorder</td>
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<td>Bronchospasm</td>
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<td>Bronchiolitis</td>
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<td></td>
<td>Rhinitis</td>
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<td>FR-2013-3306</td>
<td>Bronchiolitis</td>
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<td>FR-2012-3754</td>
<td>Onset of medical contraindication</td>
<td>No</td>
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<td>FR-2012-3970</td>
<td>Nightmare</td>
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<td>FR-2014-1442</td>
<td>Drug ineffective</td>
<td>Yes</td>
<td>Unknown (Not assessable)</td>
</tr>
<tr>
<td></td>
<td>Off label use</td>
<td>Yes</td>
<td>Unknown (Not assessable)</td>
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</table>
# 2.3. SERIOUS ADVERSE DRUG REACTIONS IDENTIFIED AS IMPORTANT RISKS

The following four (4) categories of SADRs have been considered as important identified risks for this population.

Individual cases which include the following ADRs are discussed in detail in the sections below:

- **Cardiac disorders**: bradycardia and prolonged atrio-ventricular conduction or intensification of an AV block
- **Vascular disorders**: hypotension
- **Respiratory disorders**: bronchospasm and bronchial hyperreactivity reactions
- **Metabolism and nutritional disorders**: hypoglycaemia and related seizures

<table>
<thead>
<tr>
<th>Propranolol oral solution 3.75 mg/mL action due to Event (Case number)</th>
<th>ADRs leading to treatment dose change/ discontinuation</th>
<th>Serious</th>
<th>Causality as determined by the company</th>
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<tr>
<td>FR-2014-0616</td>
<td>Bronchiolitis</td>
<td>Yes</td>
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<td>FR-2014-0644</td>
<td>Bronchiolitis</td>
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<td>FR-2014-1623</td>
<td>Bronchiolitis</td>
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<td>FR-2014-1996</td>
<td>Bronchiolitis</td>
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<tr>
<td>FR-2014-2175</td>
<td>Gastroenteritis Sleep disorder</td>
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<td>FR-2014-2569</td>
<td>Bronchiolitis Lung disorder Asthma</td>
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<td>FR-2014-1997</td>
<td>Failure to thrive Decreased appetite</td>
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<td>FR-2014-0982</td>
<td>Hypoglycaemia Intentional dug misuse</td>
<td>Yes</td>
<td>Possible</td>
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<td>FR-2013-3630</td>
<td>Nightmares</td>
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<td>Nightmares</td>
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<tr>
<td>FR-2014-1013</td>
<td>Choking Asthma</td>
<td>Yes</td>
<td>Not suspected</td>
</tr>
</tbody>
</table>

Source: Cumulative Summary Tabulation of Events and Line Listing of cases covering: 13-Apr-2010 to 12-Oct-2012 and narratives

1 The patient died
2.3.1. CARDIAC DISORDERS

Cumulatively, 3 cases of bradycardia and one case of atrio-ventricular block associated to acute cardiac failure have been reported.

➔ FR-2011-1487: AV block complete / Acute cardiac failure (fatal)

A 5-month-old female patient with painful ulcerated infantile hemangioma on the back experienced Grade III atrio-ventricular block and heart failure leading to death, while she was receiving propranolol oral solution 3.75 mg/mL, and several other concomitant suspect drugs.

The patient was born at term, at 41 weeks of amenorrhea. She presented with biliary atresia diagnosed at 6 weeks of age with hepatosplenomegaly, icterus, portal hypertension, without hepatocellular insufficiency. Hepatic-porto-enterostomy, performed at day 57, failed. The patient received concomitant ursodeoxycholic acid, tocofersolan, vitamin K and injectable vitamins. From 31-May-2011, she was hospitalized due to edematous-ascitic decompensation. She received enteric nutrition with constant flow, and treatment with Aldactone® (spironolactone) and albumin.

There was no contraindication to starting treatment with propranolol oral solution 3.75 mg/mL. Prior to treatment, a cardiopediatrician had performed a clinical examination, including electrocardiogram (ECG) (QTc 430 milliseconds, QRS axis 64, PR 124 milliseconds, and no conduction disorders) and a cardiac echography (which showed isolated increased of cardiac flow without diastolic surcharge, no arterial pulmonary hypertension).

Propranolol was initiated on 9-Jun-2011 at a dose of 1 mg/kg/day, increasing to 2 mg/kg/day on 12-Jun-2011. During treatment, daily ECGs under propranolol oral solution 3.75 mg/mL had been unremarkable. On 17 Jun 2011, an oeso-gastroduodenal fibroscopy was performed for pre-transplant screening and revealed esophageal varices and portal hypertension gastritis.

On 22-June-2011, a prophylactic sclerotherapy was planned under general anesthesia with propofol, suxamethonium, sevoflurane and sulfentanil. Fibroscopy revealed grade III varices with red threatening signs. It was impossible to pass the Killian's triangle to perform elastic ligature of esophageal varices. Therefore an endoscopic sclerosis was performed in 5 points with total administration of 12.5 ml of Aetoxisclerol (lauromacrogol 400, 2% diluted). Then, octreotide was given in continuous intravenous infusion to help decrease bleeding.

About 15 minutes after last lauromacrogol injection, the patient experienced bradycardia, quickly worsening, corresponding to atrioventricular block grade I, then grade II and grade III, with circulatory failure, a fall in blood pressure and in end-tidal CO₂. Resuscitation measures were performed with external cardiac massage and administration of adrenaline, in bolus (10 gamma/kf x3), then continuously until 3mg/h after failure of isoprenaline. A rhythm of ventricular escape under 40/min persisted and a transcutaneous external pacing (until 140mA) failed. The patient presented with transient asystole.
In emergency, a 5-Fr bipolar pacing catheter was set up by internal right jugular guidance leading to efficient cardiac stimulation with paced ventricular complexes in VVI mode. The patient became stable hemodynamically with a normal arterial pressure, a SPO₂ at 100% and normal ETCO₂.

The patient was admitted to the intensive care unit with intubation and ventilation, whilst continuing the previous treatment. After a temporary hemodynamic stabilization with a rhythm at 90 bpm in VVI mode, the patient condition worsened at 05:00 pm, with the occurrence of ventricular escape complexes at 40/min despite heart rate at 102 bpm on ECG. Transthoracic ECG identified severe biventricular dysfunction with down low left ventricular ejection fraction and diffuse hypokinesis excluding apex.

The patient died and no autopsy was performed.

The exact timeline between the last administration of propranolol and the occurrence of the reactions was unknown. Propranolol blood level, at the time of the reactions, showed that the concentration was within the therapeutic range. There were no known interactions with co-administered drugs. Considering other suspect drugs that the patient was taking, sufentanil and propofol both carry a risk of bradycardia, atrio-ventricular block, and arrhythmia until cardiac arrest. Of note, a case of heart failure has been published after endoscopic sclerotherapy (as performed for this patient) of variceal bleeding in a 63-year-old male patient due to the action of the drug passing into the systemic circulation from the site of injection (*Paterlini, The Lancet, June 2, 1984*); A literature search did not allow identifying information on interaction between propranolol and lauromacrogol (other suspect treatments for this patient administered for sclerotherapy).

The causal relationship between the reported reactions and propranolol oral solution 3.75 mg/mL treatment was considered doubtful by both Pierre Fabre and the Health Authority, considering the cardiac safety monitoring since propranolol introduction, the underlying diseases, the numerous concomitantly taken medicines and therapeutic endoscopic procedure.
FR-2011-0664: Bradycardia / Sinus arrest

A 4-month-old female patient experienced bradycardia and cardiac sinusal break while she was receiving propranolol oral solution 3.75 mg/mL. At D7, while she was under continuous ECG surveillance by cardioscope, the nurse identified two episodes of tachycardia at 200/min during sleeping. Considering the titration, the dose was increased to 2 mg/kg/day by the physicians and a 24-hour Holter monitoring was planned. It was performed 3 days later and revealed numerous episodes of bradycardia and cardiac sinusal breaks. The patient was symptom-free during this period. Propranolol was discontinued and the patient did not receive any corrective treatment. The control Holter monitoring was normal. The patient was considered as recovered. The causal relationship of the reactions to propranolol oral solution 3.75 mg/mL treatment was considered by Pierre Fabre and Health Authority (ANSM) to be possibly related and suspected, respectively.

FR-2012-2819: Bradycardia / Hypoglycaemia

A 9-month-old male patient experienced severe bradycardia at 30 bpm related to a lack of anticipation in the treatment of a severe hypoglycaemia, the latter due to lack of treatment discontinuation during fasting period. The full narrative of this case is presented hereafter in section 2.3.4.

FR-2012-3688: Bradycardia / Hypotonia / Malaise

A one-month-old male patient (adjusted age 39 weeks), born prematurely at 34 weeks, experienced bradycardia at less than 60 bpm during one or two minutes on 14-Sep-2012, associated to symptoms of hypotonia and loss of contact. The patient had started the treatment with propranolol oral solution 3.75 mg/mL at a dose of 2 mg/kg/day on the previous day. A Holter monitoring was performed on 14-Sep-2012 and revealed a basal sinusal rhythm inaccurately betablocked, with severe hyper reflectivity. The treatment was temporarily discontinued and the events did not reoccur. The causal relationship was assessed as possible based on positive dechallenge.

2.3.2. VASCULAR DISORDERS: HYPOTENSION

Cumulatively, 4 patients have experienced hypotension with blood pressure less than 80 mmHg. These 4 cases were all assessed as possibly related to the product:

FR-2011-0698: A 3-month-old female patient experienced asymptomatic hypotension (systolic blood pressure at 70 mmHg) at D2, while she received propranolol 2 mg/kg/day. She had started the treatment the previous day at dose of 1 mg/kg/day. Propranolol was temporarily discontinued, and then reintroduced a few months later without adverse reaction. The reporter attributed the event to the young age of the patient at initiation of treatment.
FR-2012-1339: An 8-month-old male patient experienced asymptomatic hypotension (73/45 mmHg) at dose of 2 mg/kg/day (after the first administration at this dose [10 mg]). Pulse was stable (105 bpm) and there was no modification on the ECG. The dose was reduced (one dose of 7.5 mg) and then increased the following day (one dose of 10 mg), but hypotension (79/45 mmHg) recurred. The patient was discharged on that day at 5 mg BID (1 mg/kg/day), which was increased to 10 mg BID (2 mg/kg/day) on the following day and to 15 mg BID (3 mg/kg/day) 5 days later. Arterial pressure at discharge after the final dose increase was 73/48 mmHg and HR was 97 bpm, and 1 week later were 82/44 mmHg and 123 bpm, respectively.

FR-2013-1891: A 6-month-old male experienced hypotonia, pallor and hypotension with blood pressure at 75/50 mmHg one hour after each administration of Propranolol 2 mg/kg/d. The reporting physician suspected a hypoglycaemia. The treatment with Propranolol was continued without corrective treatment.

FR-2014-0691: A 3.5-month-old female patient experienced vomiting, hypotension, pallor and hypotonia following Propranolol dose increase from 1 to 2 mg/kg/d. Blood pressure dropped from 82/62 mmHg to 66/44 mmHg, then 41/20 mmHg (tachycardia at 143 bpm) and increased to 70/55 mmHg 5 minutes later, 70/43 mmHg 30 minutes later and then 97/77 mmHg one hour later, without any associated bradycardia (Cardiac frequency at 130 BPM). Capillary glycaemia monitoring did not show hypoglycaemia. The treatment was continued at 1 mg/kg/day without any associated adverse reactions. Cardiac examination was normal. The reporting physician suspected a vasovagal episode.

Among these 4 cases, the patients were asymptomatic in 2 cases and 2 patients experienced pallor, hypotonia and/or vomiting. All the patients were reported as having recovered or being recovering. The reactions required temporarily discontinuation of the treatment in only one case. In the other 3 cases, the reaction did not require the discontinuation of the treatment with Propranolol.

2.3.3. RESPIRATORY DISORDERS: BRONCHOSPASM AND BRONCHIAL HYPERREACTIVITY REACTIONS

During the clinical development, 11 adverse events grouped under the term of bronchospasm, 29 adverse events grouped under the term of bronchiolitis and 46 adverse events grouped under the term of bronchitis were observed in 424 patients treated in the clinical studies involving thus respectively 2.6%, 6.8% and 10.8 % of patients. Bronchial hyperreactivity is a direct effect of non-beta selectivity of Propranolol, resulting in bronchospasm due to pulmonary beta 2-blockade.
As in the latest bridging report, the database was queried for cases with the following adverse event PTs (Preferred Terms) (MedDRA version 17.1): “bronchospasm”, “bronchiolitis” and “bronchitis”. Moreover, following the review of this strategy, the PTs “respiratory syncytial virus bronchiolitis” and “asthma” were added in this query.

Using this new strategy, 51 cases with 55 ADRs have been reported in the compassionate use programme. Among these 51 cases of respiratory disorders, 18 cases have been assessed as serious.

- Six (6) cases of bronchospasm:

These 6 cases of bronchospasm have been assessed as serious.

-Two (2) cases of bronchospasm were assessed as possibly related to the product based on positive dechallenge:

→ FR-2013-0358: After 7 months of treatment with Propranolol 3 mg/kg/day, an 11-month-old female patient (born prematurely at 27 weeks) presented with marked dyspnea, asthenia and body temperature at 37.7 °C, which required hospitalization. Pulmonary examination revealed sonorous rales and few sibilant rales without crepitants. Respiratory syncytial virus test was positive. The treatment was temporarily discontinued and corrective treatment included fluticasone, salbutamol and budesonide. It is to be noted that the patient had a past medical history of infantile asthma, secondary to bronchopulmonary dysplasia.

→ FR-2013-3235: A 4-month-old female patient experienced several episodes of bronchiolitis associated with bronchospasm following increase of the dose from 1 mg/kg/day to 2 mg/kg/day and then 3 mg/kg/day. The treatment with Propranolol was discontinued and the patient recovered.

-Two (2) cases of bronchospasm were assessed as doubtfully related to the product. In both cases, dechallenge was inconclusive, the treatment having been continued and the patient receiving supportive treatment.

→ FR-2011-0752: Two months after the initiation of treatment with Propranolol 2 mg/kg/d, a 6-month-old female patient experienced bronchiolitis associated with bronchospasm, requiring treatment discontinuation and corrective treatment. At the date of last follow up, the patient was recovering.

→ FR-2011-0326: After two and a half months of treatment with Propranolol 2.5 mg/kg/day for a life-threatening subglottic haemangioma, a 6-month-old female patient experienced bronchospasm (sibilant rhonchus) in an infectious context. Chest X-ray was normal. The dose was decreased.
-Moreover, 2 poorly documented serious cases of *bronchospasm* have been reported for which the causal relationship was not assessable (FR-2013-1986, FR-2013-1987). These cases were reported on the D5 form “Treatment discontinuation”, and no more information was available despite several requests. These cases were assessed as serious, as bronchospasm is a medically significant adverse event. In these 2 cases, the treatment was discontinued.

- Thirty-seven (37) cases of *bronchiolitis* (without bronchospasm)

Among these 37 cases, 12 cases of bronchiolitis have been assessed as serious. Among these serious cases, 1 case was associated with *a circulatory shock* and *respiratory arrest* and 4 cases were associated with *respiratory distress*. These 5 worth mentioning cases are detailed below:

- **One (1) case of bronchiolitis with circulatory shock and respiratory arrest:**

  ➔ **FR-2011-0467:** A 6-month-old female patient with haemangioma on eyelid, disturbing the vision started Propranolol 1 mg/kg/d. The dose was not increased due to episode of non-serious bronchiolitis. Her condition aggravated in the following days and she experienced circulatory shock and respiratory distress. The baby was intubated and ventilated. After 10 days of monitoring, she fully recovered without sequel. Propranolol was discontinued and not reintroduced. These reactions were assessed as possibly related to the product.

- **Four (4) cases of bronchiolitis with respiratory distress:**

  ➔ **FR-2012-0556:** Two months after the initiation of Propranolol 3 mg/kg/day for an upper lip infantile haemangioma, a 7-month-old male patient experienced a first episode of non-serious bronchiolitis. Propranolol was discontinued for one week. The patient experienced a second serious episode with respiratory distress leading to hospitalisation. Propranolol was discontinued at this time, two days after the first signs of respiratory disorder and cough. He experienced a third episode, also requiring hospitalisation. This one occurred while the patient was propranolol free. These reactions were assessed as possibly related to the product.

  ➔ **FR-2013-0259:** A 6-month-old female patient experienced an episode of bronchiolitis 3 months after treatment initiation with Propranolol 2 mg/kg/day for forehead haemangioma. She experienced respiratory distress with struggle to breath (including in drawing, thoraco-abdominal seesaw). Respiratory auscultation revealed bilateral crepitant rales and pulmonary computed tomography scan showed bronchial syndrome. Respiratory syncytial virus test was positive. The treatment was discontinued and corrective treatment included salbutamol and nasopharyngeal unclogging. The outcome was favourable. Respiratory distress was assessed as possibly related to the treatment, and bronchiolitis was assessed as doubtfully related to the treatment, based on positive respiratory syncytial virus test.
FR-2013-1745: A 7-month-old male patient experienced respiratory distress and dyspnea 3 months after the initiation of the treatment with Propranolol 2 mg/kg/day for eyelid haemangioma. At admission, he presented with diffuse sibilant rales in both lungs and oxygen saturation at 92%. To be noted that the patient had past medical history of 2 previous episodes of bronchiolitis. Corrective treatment included salbutamol and ipratropium. The treatment was definitely discontinued. These reactions were assessed as doubtfully related to the treatment based on inconclusive chronology.

FR-2014-1118: A 4-month-old female patient experienced acute infantile respiratory syncytial virus bronchiolitis secondarily infected by Haemophilus after 2 and half months of treatment with Propranolol 2 mg/kg/d. She presented with signs of respiratory distress. Respiratory syncytial virus test was positive and chest X-ray showed opacity of the average lobe. Propranolol was discontinued during 3 days and the course was favourable after antibiotherapy and transient oxygenotherapy. These reactions were assessed as doubtfully related to the treatment.

Conclusion concerning cases of bronchiolitis:

Importantly, these 5 cases of bronchiolitis associated with respiratory disorders all occurred during wintertime, season of high prevalence for viral upper respiratory tract infections. Propranolol PFD oral solution, by its bronchoconstrictive properties, may have aggravated the respiratory condition of the patient, in a context of viral bronchiolitis.

Among the 37 cases of bronchiolitis, bronchiolitis was the only reported ADR in 29 cases, among which 5 were considered as serious (FR-2010-2869, FR-2011-0777, FR-2011-1422, FR-2013-1066, FR-2014-0616). In 2 cases, bronchiolitis was associated with asthma (FR-2014-2569 and FR-2012-2236).

- Seven (7) cases of bronchitis

Seven (7) non-serious cases of bronchitis have been reported since the first authorization (FR-2011-0646, FR-2012-1919, FR-2012-3346, FR-2013-0865, FR-2013-1081, FR-2013-2500, FR-2014-1152). One of these cases of bronchitis was associated to a rhinopharyngitis and 3 were described as asthmatiform bronchitis.

- One (1) case of asthma (without bronchiolitis)

FR-2014-1013: A 12-month-old female patient experienced asthma which required discontinuation of the treatment with Propranolol after 11 months of treatment at 0.2 mg/kg/day. Moreover, the patient died due to choking on food 2 months after the end of the treatment. The causal relationship between Propranolol and asthma was assessed as doubtful. Additional information is expected to properly assess this case. The causal relationship between Propranolol and death due to choking on food was assessed as not related.
Conclusion concerning all cases of respiratory disorders:

Among these 51 cases of respiratory disorders, **18 cases have been assessed as serious**: 6 cases of bronchospasm (1 was associated with bronchiolitis in a prematurely born female patient), 12 cases of bronchiolitis (3 associated with respiratory distress and 1 associated with circulatory shock and respiratory arrest and 1 associated with asthma).

At the time of reaction onset, patient’s age was between 2.5 months and 17 months. Most of these cases of respiratory disorders occurred during wintertime (32/51), most of which several months after treatment introduction; posology at the time of onset was 1 mg/kg/day for 7 cases, 2 mg/day for 31 cases, 2.5 mg/kg/day for 1 case, 3 mg/kg/day for 6 cases, and unknown in 6 cases.

In twenty-one (21) cases the treatment was definitely discontinued, in 15 the treatment was temporarily discontinued, in 7 the treatment was not discontinued during respiratory disorders, in 1 case the dose was decreased, in 1 case the ATU renewal was refused, and in 6 cases, action taken was unknown.

To conclude, most of these episodes of respiratory disorders occurred during wintertime (32/51) and were of infectious origin. Bronchial hyperreactivity is a direct effect of non-beta selective propranolol, resulting in a bronchospasm due to pulmonary beta 2-blockade. Propranolol PFD oral solution, by its bronchoconstrictive properties, may have aggravated the respiratory condition of the patient, in a context of viral bronchiolitis. No new information became available concerning this important identified risk.
2.3.4. METABOLISM AND NUTRITIONAL DISORDERS: HYPOGLYCAEMIA AND HYPOGLYCAEMIC SEIZURE

Cumulatively, a total of 9 cases of hypoglycaemia including 2 cases of hypoglycaemic seizure have been reported:

- 4 serious cases of hypoglycaemia (FR-2010-1786, FR-2011-3402, FR-2013-1360 and FR-2014-0982),
- 2 serious cases of hypoglycaemic seizure (FR-2012-0275 and FR-2012-2819)
- 3 non-serious cases of hypoglycaemia (FR-2013-2204, FR-2013-1891 and FR-2014-1119)

The most frequently associated symptoms were alteration of consciousness, hypotonia, pallor, hyperhydrosis and somnolence.

**Serious cases:**

- **FR-2010-1786:** A 5-month-old male patient experienced an episode of hypoglycaemia of 1.1 mmol/L (0.20g/L) after the first intake of Propranolol PFD at a dose of 1 mg/kg/day. The patient was symptom-free. The event rapidly resolved after feeding and a perfusion of glucose 10 %. As the patient was hospitalized for this treatment initiation, the dose was increased to 2 mg/kg/d at the 4th or 5th day after treatment initiation. The causality was assessed as possible.

- **FR-2011-3402:** A 15-month-old female patient started Propranolol PFD, 1 mg/kg/day. In consultation, one week later, hypoglycaemia was discovered (fasting blood glucose level at 0.4g/L). Parents reported that the infant had experienced asthenia and excessive sleepiness during the first week of treatment and the physician considered this state as probably related to hypoglycaemia. The patient had not experienced infectious episode or concurrent disease and there had been no reduction in food intake. Propranolol was definitely discontinued. Sugar was given as corrective treatment. The patient completely recovered. The causality was assessed as possible.

- **FR-2013-1360:** The treatment with Propranolol PFD 2mg/kg/d of a 6-month-old male patient was not discontinued during an episode of rotavirus infection including fever, diarrhoea, and a significant decrease in food intake (no vomiting). On 27-Apr-2013, the patient had cold extremities, was pale, with fixed stare and hypertonic movements. A glucose test revealed severe hypoglycaemia (result unknown). The patient was hospitalized until 11-May-2013 and received glucose at 30 %. On an unknown date after Chlorhydrate de Propranolol discontinuation, the patient experienced 2 more episodes of hypoglycaemia with glycemia index at 0.56 and 0.44 g/l. An endocrine test, the metabolic investigations and MRI were therefore performed and revealed a growth hormone deficit. Causality was assessed as possible.
→ **FR-2012-0275:** An 8-month-old female patient, experienced *hypoglycaemic seizure* described as convulsions in sleep and deep hypoglycaemia, 6 months after the beginning of the treatment with Propranolol PFD, 1.8 mg/kg/ day. The patient was admitted in paediatric emergency medicine unit and received glucose 30 %. Hypoglycaemia followed a period of fasting and vomiting in a context of acute gastroenteritis to Norovirus and ENT virosis. Importantly, propranolol had not been temporarily discontinued as it is recommended in case of difficulties to feed the infant. Causality was assessed as possible.

→ **FR-2012-2819:** A 9-month-old male patient, experienced *hypoglycaemic seizure* while he was receiving Propranolol PFD at a dose of 2 mg/kg/ day, 6 months after the beginning of the treatment. He had received the treatment one evening while he had not eaten his full evening ration of milk and the following morning while he had not eaten. He presented with tonic-clonic generalised convulsions and was kept to hospital by an emergency team. Unfortunately, the blood glucose was not determined and the patient’s state deteriorated despite treatment with clonazepam, until severe bradycardia requiring resuscitation measures. Chlorhydrate de Propranolol treatment was definitely discontinued. The causality was assessed as possible.

→ **FR-2014-0982:** An 11-month-old male patient experienced hypoglycaemia with malaise, sweat, pallor, hypotonia and somnolence in a context of fasting and vomiting. The treatment had not been discontinued during an episode of gastroenteritis that was considered as a misuse. Propranolol was discontinued and corrective treatment included glucose (glucose 5%) and NaCl 10% perfusion. The patient recovered. According to the Therapeutic information, treatment with Propranolol must be discontinued during fasting or gastroenteritis (including vomiting), in order to avoid hypoglycaemia. The causality was assessed as possible.

**Non-serious cases:**

Moreover, 3 non-serious cases of *hypoglycaemia* (FR-2013-2204, FR-2013-1891 and FR-2014-1119) have been reported. In the first 2 cases, the patients presented associated signs of *pallor* and *hypotonia*. In the first one, the patient presented with *hypotension* and in the second one, the patient presented with *hyperhydrosis* and *somnolence*. In the third case, the patient was asymptomatic. The 3 cases were assessed as possibly related to the treatment, as they occurred during the hour following each administration. In the first 2 cases, no information was provided on administration conditions such as concomitant fasting, vomiting or infection such as gastroenteritis. In the third case, the reaction occurred in a context of regurgitation and poor food intake.
Conclusion:

Out of these 9 cases of hypoglycaemia/hypoglycaemic seizure, 4 serious cases occurred while the treatment had not been administered in accordance with the protocol for therapeutic use. In fact, the patients were experiencing an infectious episode (diarrhea or vomiting), or were in a period of low food intake and/or fasting, but the treatment had not been temporarily discontinued. In one case the parents gave the dose twice by mistake.

In none of these cases, information was available on any previous or concomitant treatments with corticosteroids which may have induced adrenal suppression (that may result in the loss of the counter regulatory cortisol response which increases the risk of hypoglycaemia).

These cases emphasize the need to educate parents and relatives on the risk of hypoglycaemia during treatment with Propranolol PFD oral solution, and on the appropriate actions to be taken when the child presents the first signs of hypoglycaemia such as somnolence, pallor, hypotonia as well as during periods of fasting.

Thereby, severe consequences of hypoglycaemia, such as seizures, could have been avoided in the 2 cases of hypoglycaemic seizure, if the treatment had been interrupted.

2.3.5. OTHER SIGNIFICANT ADVERSE DRUG REACTIONS

Other significant ADRs worth mentioning include height and/or weight gain delay, potential risk of administration error and vasoconstriction:

- **Height and/or weight gain delay**

  Cumulatively, 7 cases of height and/or weight gain delay have been reported. One case has been assessed as serious and 6 cases have been assessed as non-serious:

  **Serious case:**

  → FR-2011-0991: A 6-month-old female patient, not born prematurely, experienced weight stagnation in a context of alimentary refusal, vomiting and respiratory discomfort after 2 and half months of treatment with Propranolol 1 mg/kg/day for hyperalgic ulcerated tuberous hemangioma. Investigations, including coeliac disease test, malabsorption and allergic tests for proteins of cow milk and/or in wheat were unremarkable. The patient received enriched milk and she recovered while Propranolol was continued. Weight stagnation was assessed as doubtfully related to the product.

  **Non-serious cases:**
→ FR-2013-1219: An 8-month-old female patient, not born prematurely, experienced growth delay in height and weight noticed one month after the end of the treatment in a context of low food intake. She had been treated with Propranolol for 2 and half months. Nine (9) months later, the patient had not recovered despite introduction of high-protein milk. Unspecified additional examinations were ongoing at the time of the follow up report. The case was assessed as doubtfully related to the product.

→ FR-2013-1994: A female patient born prematurely at 28 weeks of amenorrhea, with hypotrophy at birth and Turner’s syndrome, experienced decreased weight gain in a context of decreased appetite after 5 months of treatment with Propranolol. The case was assessed as doubtfully related to the product.

→ FR-2013-2088: A 1-year-old female patient, not born prematurely, experienced failure to thrive, and weight gain stagnation after one month of treatment with Propranolol. Propranolol was discontinued and then re-introduced. The patient recovered on an unspecified date. No information about complementary exams was available despite requests. The case was assessed as doubtfully related to the product.

→ FR-2014-1312: A 6-month-old female patient, not born prematurely, experienced weight stagnation after 10 days of treatment with Propranolol. Propranolol was continued. No complementary exams were performed. The outcome was not provided despite requests. The case was assessed as doubtfully related to the product.

→ FR-2014-1621: A 4-month-old female patient, not born prematurely, experienced anorexia and shift in the height-weight curve after one month and a half of treatment with Propranolol. Propranolol was discontinued and she received oral food supplement. The patient gained weight while she still experienced difficulties in eating. Propranolol was re-introduced; however, the outcome remained unknown. No information about complementary exams was available. The causal relationship could not be assessed due to a lack of information.

→ FR-2014-1997: A 7-month-old female patient, not born prematurely, experienced decrease in appetite and shift in the height-weight curve after 17 days of treatment with Propranolol. Gastroenterological work-up was negative, research for anti-transglutaminase antibodies was negative, complete blood count, blood electrolytes, prothrombin, liver work-up, thyroid work-up and ferritin were normal. Propranolol was discontinued and the patient was recovering on an unspecified date. Complementary examinations to exclude other etiologies such as impaired metabolism (chromosomal abnormality (eg, Down syndrome, Turner syndrome), fructose intolerance, galactose-1-phosphate uridyl transferase deficiency (classic galactosemia), inborn errors of metabolism) or increased excretion (diabetes, proteinuria) were not performed. The case was assessed as doubtfully related to the product.
Conclusion:

Cumulatively, 7 cases of height and/or weight gain delay have been reported of which 4 involved a poor height gain. All but one case were assessed as non-serious. Only one patient was born prematurely. Decreased or low food intake was reported in 4 cases.

In 2 cases, an alternative cause may explain the growth delay (FR-2011-0991: alimentary refusal, while the patient was presenting aggravated respiratory discomfort and FR-2013-1994: hypotrophy at birth and Turner’s syndrome). In 5 other cases, results of complementary exams to exclude an alternative etiology were not available or the complementary exams were not performed.

At the time of follow-up reports, all patients had regained appetite. Four (4) patients had caught up height and weight results. However, for 1 patient, weight gain remained poor and weight curve remained below normal (FR-2013-1219), and the outcome remains unknown in 2 cases (FR-2014-1312 and FR-2014-1621).

Of note, all these 7 cases concerned female patients. However, it may be explained by the fact that female sex is a known risk factor for the development of IH (female to male ratio of 2.4:1). In this CUP, 75.4% of the patients included were female patients (female to male ratio of 3.1:1).

The analysis of these cases with the presence of alternative explanations or the absence of search of alternative aetiologies did not allow establishing a causal relationship between Propranolol and height and/or weight gain delay. However, long-term effects including on growth was considered as missing information in the risk management plan of the European application dossier.

- Potential risk of administration error

Cumulatively, 8 cases of administration error have been reported. Two (2) cases have been assessed as serious and 6 cases have been assessed as non-serious:

Serious cases:
Among these 8 cases, 2 serious cases concerned patients who experienced hypoglycaemic seizure and bradycardia in one case, and hypoglycaemia in the other case, while Propranolol was not discontinued during a fasting period (FR-2012-0275 and FR-2014-0982: These cases are detailed in Section 2.3.4).
Non-serious cases:

-Two (2) cases concerned errors due to an inappropriate use of the syringe without occurrence of adverse reaction: one case concerned administration with a syringe of another product and one case concerned confusion between mg and mL when using the syringe.
-Two (2) cases concerned drug dose omissions,
-One (1) case concerned an accidental double administration (by two different persons) without adverse reaction
-One (1) case concerned a patient who received 1mg/kg.day, 3 times daily and who experienced cold extremities.

To conclude, the potential risk of administration error was considered as an important potential risk in the risk management plan of the European application dossier. The potential risks of administration error to be considered are those linked to an error in the administered dose per intake that needs to be adjusted during the treatment course: firstly during treatment titration, then with the evolution of patient’s weight.

- Vasoconstriction

Cumulatively, a total of 6 non-serious cases of vasoconstriction/ Raynaud’s syndrome have been reported during the compassionate use program. The patients experienced a non-serious adverse event of vasoconstriction at a variable time to onset of the reaction since the first treatment administration (from 3 days to 8 months after the first administration). The causal relationship was assessed as possible for 4 cases (based on suggestive chronology and positive dechallenge and/or rechallenge), and doubtful for 2 cases (based on the positive outcome despite treatment continuation).

Literature review retrieved a case of acrocyanosis, nail dystrophy, and small digital infarcts in a 2-week-patient treated during 16 months with Propranolol at a dose of 1 mg/kg/day for infantile haemangioma (Metry et al.² 2012). Propranolol worsened peripheral arteriopathy with digital infarcts and severe sleep disturbance led to decease. According to the authors, although the role of Propranolol in these peripheral soft-tissue findings cannot be certain, Propranolol induced effects on peripheral vasculature. This effects include low cardiac output and unopposed alpha-adrenergic drive, result in low extremity blood flow. This mechanism leads to the commonly observed side effects of cold extremities and Raynaud’s phenomenon.

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To conclude, vascular disorders with peripheral coldness and Raynaud’s syndrome were considered as a non-important identified risk. Currently, peripheral coldness and Raynaud’s syndrome are listed events in the reference safety document of the Protocol for Therapeutic Use of Propranolol PFD. It is to be noted that the 4.8 section of this reference safety document is based on the SPC of Propranolol tablets for adults, which include peripheral coldness and Raynaud’s syndrome.

2.4. DATA FROM LITERATURE ON SAFETY OF THE USE OF PROPRANOLOL IN INFANTS

On 20th April 2010, Pierre Fabre Corporate Vigilances Division initiated a literature review on publications presenting any information on safety, i.e., at least one AE reported (databases searched: Excerpta Medica and Medline).

These publications include results obtained with off-label use of various propranolol preparations.

Up to 31st July 2014, 69 publications concerning 1541 patients with IH and treated with propranolol have been selected (of note, some abstracts and posters available were not included in this analysis due to the lack of quantifiable safety data).

The majority of patients were treated with 2 mg/kg/day (range 1-4 mg/kg/day except for 1 publication in 3 patients receiving higher doses [Rosbe 2010]), for durations up to 30 months. A summary of patient exposure is presented in Table 18.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Year</th>
<th>No. Treated with Propranolol</th>
<th>Dose of Propranolol</th>
<th>Mean Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>2010</td>
<td>3</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Al Dhaybi</td>
<td>2011</td>
<td>18</td>
<td>2-3 mg/kg/day</td>
<td>Until 1 year of age</td>
</tr>
<tr>
<td>Bagazgoitia</td>
<td>2011</td>
<td>71</td>
<td>2 mg/kg/day</td>
<td>At least 12 weeks</td>
</tr>
<tr>
<td>Balma-Mena</td>
<td>2012</td>
<td>44</td>
<td>2-3 mg/kg/day</td>
<td>7.3 months</td>
</tr>
<tr>
<td>Belen</td>
<td>2014</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bernabeu-Wittel</td>
<td>2011</td>
<td>28</td>
<td>2 mg/kg/day</td>
<td>8.7 months (2-16 months)</td>
</tr>
<tr>
<td>Bertrand1</td>
<td>2011</td>
<td>12</td>
<td>2.7 mg/kg/day (2.5-3.5 mg/kg/day)</td>
<td>10.6 months</td>
</tr>
<tr>
<td>Bertrand2</td>
<td>2012</td>
<td>35</td>
<td>2-3 mg/kg/day</td>
<td>8.9 (1-13 months)</td>
</tr>
<tr>
<td>Betlloch-Mas</td>
<td>2012</td>
<td>20</td>
<td>2 mg/kg/day</td>
<td>3-14 months</td>
</tr>
<tr>
<td>Blatt</td>
<td>2011</td>
<td>54</td>
<td>1-4 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bonifazi</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>10 months</td>
</tr>
<tr>
<td>Bozemani</td>
<td>2012</td>
<td>1</td>
<td>1 mg/kg/day</td>
<td>30 weeks</td>
</tr>
<tr>
<td>Breur</td>
<td>2011</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Broek</td>
<td>2013</td>
<td>5</td>
<td>2-3 mg/kg/day</td>
<td>1 to 19 months</td>
</tr>
<tr>
<td>Buckmiller</td>
<td>2010</td>
<td>32</td>
<td>2 mg/kg/day</td>
<td>5.5 months (2-10 months)</td>
</tr>
<tr>
<td>Cavalli</td>
<td>2012</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>At least 6 months</td>
</tr>
<tr>
<td>Publication</td>
<td>Year</td>
<td>No. Treated with Propranolol</td>
<td>Dose of Propranolol</td>
<td>Mean Duration of Treatment</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Chai</td>
<td>2011</td>
<td>27</td>
<td>2 mg/kg/day</td>
<td>3.83 months (2.75-5.75 months)</td>
</tr>
<tr>
<td>Chik</td>
<td>2010</td>
<td>12</td>
<td>2 mg/kg/day</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Corapcioglu</td>
<td>2011</td>
<td>12</td>
<td>2 mg/kg/day</td>
<td>5 months (4-9 months)</td>
</tr>
<tr>
<td>Dotan</td>
<td>2013</td>
<td>1</td>
<td>3 mg/kg/day</td>
<td>-</td>
</tr>
<tr>
<td>Dyme</td>
<td>2012</td>
<td>15</td>
<td>3 mg/kg/day</td>
<td>2.8 months (0.2-10 months)</td>
</tr>
<tr>
<td>El-Essawy</td>
<td>2011</td>
<td>15</td>
<td>2 mg/kg/day</td>
<td>7.67 ±3.96 months</td>
</tr>
<tr>
<td>Erbay</td>
<td>2010</td>
<td>16</td>
<td>2 mg/kg/day</td>
<td>1.5-6.5 months</td>
</tr>
<tr>
<td>Fode</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fuchsmann</td>
<td>2011</td>
<td>39</td>
<td>2 mg/kg/day</td>
<td>8.5 months (33/39 pts)</td>
</tr>
<tr>
<td>Fusili*</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Frost</td>
<td>2013</td>
<td>1</td>
<td>0.5 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Georgountzou</td>
<td>2012</td>
<td>28</td>
<td>2 mg/kg/day</td>
<td>7.56 months (2.5-16 months)</td>
</tr>
<tr>
<td>Giron-Vallejo</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>Approximately 6 months</td>
</tr>
<tr>
<td>Graafl de</td>
<td>2011</td>
<td>28</td>
<td>1.8-4 mg/kg/day</td>
<td>4.5-17 months</td>
</tr>
<tr>
<td>Haider</td>
<td>2010</td>
<td>17</td>
<td>2 mg/kg/day</td>
<td>Until complete resolution or regression to point of eliminating visual compromise, or at 9 to 11 months of age</td>
</tr>
<tr>
<td>Harper</td>
<td>2011</td>
<td>30</td>
<td>2 mg/kg/day</td>
<td>To 1 year of age</td>
</tr>
<tr>
<td>Hasan</td>
<td>2013</td>
<td>36</td>
<td>3 mg/kg/day</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Hermans</td>
<td>2011</td>
<td>20</td>
<td>2.0-2.5 mg/kg/day</td>
<td>9.1 months (in 19 patients)</td>
</tr>
<tr>
<td>Hogeling</td>
<td>2011</td>
<td>19</td>
<td>2 mg/kg/day</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Holland</td>
<td>2010</td>
<td>3</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Holmes</td>
<td>2011</td>
<td>31</td>
<td>3 mg/kg/day</td>
<td>12.5 weeks (1-58 weeks)</td>
</tr>
<tr>
<td>Hsu</td>
<td>2012</td>
<td>13</td>
<td>2-3 mg/kg/day</td>
<td>5 (3.14) months for 6/13 infants</td>
</tr>
<tr>
<td>Jannmohamed</td>
<td>2011</td>
<td>2</td>
<td>2 mg/kg/day; 1.5 mg/kg/day</td>
<td>At least 9 weeks</td>
</tr>
<tr>
<td>Javia</td>
<td>2011</td>
<td>12</td>
<td>2 mg/kg/day</td>
<td>At least 2 days</td>
</tr>
<tr>
<td>Jian</td>
<td>2013</td>
<td>97</td>
<td>2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Koay</td>
<td>2011</td>
<td>2</td>
<td>1-1.5 mg/kg/day</td>
<td>5 months/unknown</td>
</tr>
<tr>
<td>Küpeli</td>
<td>2012</td>
<td>14</td>
<td>2 mg/kg/day</td>
<td>Infants: at least 12 months</td>
</tr>
<tr>
<td>Lawley</td>
<td>2009</td>
<td>2</td>
<td>2 mg/kg/day</td>
<td>&gt;1 year of age: at least 6 months</td>
</tr>
<tr>
<td>Leboulanger</td>
<td>2010</td>
<td>14</td>
<td>2.5 mg/kg/day</td>
<td>At least 6 months</td>
</tr>
<tr>
<td>Lv</td>
<td>2012</td>
<td>37</td>
<td>2 mg/kg/day</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Manunza</td>
<td>2010</td>
<td>30</td>
<td>2 mg/kg/day</td>
<td>Completed (19): 7 months (3.5-15 months)</td>
</tr>
<tr>
<td>Marsciani</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>At least 1 month</td>
</tr>
<tr>
<td>Metry</td>
<td>2013</td>
<td>32</td>
<td>1.8 mg/kg/day</td>
<td>12.3 months (in 19/32 completers)</td>
</tr>
<tr>
<td>Missoi</td>
<td>2011</td>
<td>17</td>
<td>2 mg/kg/day</td>
<td>Median 6.8 months</td>
</tr>
<tr>
<td>Malik</td>
<td>2013</td>
<td>10</td>
<td>2-3 mg/kg/day</td>
<td>3 months</td>
</tr>
<tr>
<td>Ozyoruk</td>
<td>2014</td>
<td>14</td>
<td>2 mg/kg/day</td>
<td>3 to 12 months</td>
</tr>
<tr>
<td>Pavlakovic</td>
<td>2010</td>
<td>1</td>
<td>2 mg/kg/day</td>
<td>5 months</td>
</tr>
<tr>
<td>Phillips</td>
<td>2012</td>
<td>188</td>
<td>2 mg/kg/day</td>
<td>8 months (10-30 months)</td>
</tr>
<tr>
<td>Price</td>
<td>2011</td>
<td>68</td>
<td>2 mg/kg/day</td>
<td>7.9 months (3.5-14.0 months)</td>
</tr>
<tr>
<td>Roshe</td>
<td>2010</td>
<td>3</td>
<td>3-6 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Saint-Jean</td>
<td>2011</td>
<td>33</td>
<td>2-3 mg/kg/day</td>
<td>5.9 months</td>
</tr>
<tr>
<td>Sans</td>
<td>2009</td>
<td>32</td>
<td>2-3 mg/kg/day</td>
<td>6.1 months</td>
</tr>
<tr>
<td>Santos</td>
<td>2010</td>
<td>6</td>
<td>2 mg/kg/day</td>
<td>Variable</td>
</tr>
<tr>
<td>Schiestl</td>
<td>2011</td>
<td>25</td>
<td>2 mg/kg/day</td>
<td>10.5 months (11.4-22.1 months) in 14 completers</td>
</tr>
<tr>
<td>Schupp</td>
<td>2011</td>
<td>55</td>
<td>2 mg/kg/day</td>
<td>5.8 months</td>
</tr>
<tr>
<td>Shepherd</td>
<td>2012</td>
<td>3</td>
<td>1-2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Snir</td>
<td>2011</td>
<td>30</td>
<td>2 mg/kg/day</td>
<td>7.3 months (1.5-15.0 months)</td>
</tr>
<tr>
<td>Publication</td>
<td>Year</td>
<td>No. Treated with Propranolol</td>
<td>Dose of Propranolol</td>
<td>Mean Duration of Treatment</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>------------------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Tan</td>
<td>2011a</td>
<td>15</td>
<td>1.5-2 mg/kg/day</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tan</td>
<td>2011b</td>
<td>1</td>
<td>1.5 mg/kg/day</td>
<td>To 12 months of age</td>
</tr>
<tr>
<td>Thoumazet</td>
<td>2012</td>
<td>8</td>
<td>2 mg/kg/day</td>
<td>6.8 months (3-10 months)</td>
</tr>
<tr>
<td>Yuan</td>
<td>2014</td>
<td>9</td>
<td>1-2 mg/kg/day</td>
<td>12 months</td>
</tr>
<tr>
<td>Zegpi-Trueba</td>
<td>2012</td>
<td>57</td>
<td>2 mg/kg/day</td>
<td>7.3 months (1-24 months)</td>
</tr>
<tr>
<td>Yuan</td>
<td>2012</td>
<td>42</td>
<td>2.1 mg/kg/day (1.5-3 mg/kg/day)</td>
<td>3.6 months (1-8 months)</td>
</tr>
</tbody>
</table>

**TOTAL** 1541*

Source: respective publication.
NA: not applicable; No.: number.
1 A total of 10 of the 12 propranolol-treated patients in the Bertrand et al 2011 were also analyzed in the Bertrand et al 2012 publication. Therefore total number of patients analyzed by Bertrand et al was 37. Moreover, 2 of the 3 patients in the Shepherd et al 2012 were also analyzed in the Hogeling et al 2011.

The AEs reported in all the 69 scientific publications are presented in Table 19 by SOC and PT (as assigned by Pierre Fabre Corporate Vigilances Division).

The most frequently reported AEs were sleep disorder (62 patients), hypotension (49 patients), somnolence (31 patients), diarrhoea (29 patients), nightmares (25 patients), peripheral coldness (26 patients), bradycardia (21 patients), restlessness (16 patients), motor development delay (13 patients, in 1 publication only), bronchiolitis (11 patients) and hypoglycaemia (10 patients). All other events were reported in <10 patients each.
## Table 19: Summary of All Adverse Events Reported in Scientific Publications

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>No. of Publications with Reported AE</th>
<th>Total no. of Patients Treated with Propranolol in Reporting Publications</th>
<th>Number of Patients with AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
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<td>Abdominal discomfort</td>
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<td>Abdominal pain</td>
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<td>Gastrointestinal disorder</td>
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<td>Gastroesophageal reflux</td>
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<td>Infantile spitting up</td>
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<td>Nausea</td>
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<td>Reduced intake</td>
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<td><strong>General Disorders and Administration Site Conditions</strong></td>
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<tr>
<td>Fatigue</td>
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<td>Fever</td>
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<td>Malaise</td>
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<td><strong>Infections and Infestations</strong></td>
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<td><strong>Investigations</strong></td>
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<td><strong>Metabolism and Nutrition Disorders</strong></td>
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<td>Increased appetite</td>
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<td>Tumor lysis syndrome</td>
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<td><strong>Nervous System Disorders</strong></td>
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<td>Agitation</td>
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<td>Insomnia</td>
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<td>Motor development delay</td>
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<td>Restlessness</td>
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<td>Somnolence</td>
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<td><strong>Psychiatric Disorders</strong></td>
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<td>Abnormal behavior</td>
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<td>Anxiety</td>
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<td>Irritability</td>
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<td>Nervousness</td>
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<td>Nightmares</td>
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<td>System Organ Class</td>
<td>Preferred Term</td>
<td>No. of Publications with Reported AE</td>
<td>Total no. of Patients Treated with Propranolol in Reporting Publications</td>
<td>Number of Patients with AE</td>
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<td>---------------------------------------------</td>
<td>--------------------------</td>
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<td>--------------------------------------------------------------------------</td>
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<td>Respiratory, Thoracic and Mediastinal Disorders</td>
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<td>Asthma</td>
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<td>Breath holding</td>
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<td>Bronchial hyperactivity</td>
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<td>Bronchiolitis</td>
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<td>Bronchospasm</td>
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<td></td>
<td>Cough</td>
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<td>57</td>
<td>3</td>
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<td></td>
<td>Dyspnea</td>
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<td></td>
<td>Respiratory tract infection</td>
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<td>Stridor</td>
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<td>Tachypnea</td>
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<td>Wheezing</td>
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<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Dermatitis allergic</td>
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<td>32</td>
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<td>Eruption</td>
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<td>Exanthema</td>
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<td>Sweating</td>
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<td>Xerosis</td>
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<td>Renal and urinary disorders</td>
<td>Acute renal failure</td>
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<td>Acrocyanosis</td>
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<td>Hypotension</td>
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<td></td>
<td>Pallor</td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>Peripheral coldness</td>
<td>13</td>
<td>412</td>
<td>26</td>
</tr>
</tbody>
</table>

AE: adverse event; no.: number.

Among these 69 publications, 2 worth mentioning articles were indentified. These articles are detailed below:

- The first article (Belen et al.) presented a case report of a 2-year-old male patient with intestinal haemangiomatosis who presented with severe hyperkalaemia and was successfully managed with hydration, loop diuretics, potassium binding granules, inhaler β-2 agonists and insulin.
Propranolol was begun at a dose of 0.5 and gradually increased to 2 mg/kg/day. The patient was discharged with Propranolol full dose treatment. At the sixth month of his discharge he was symptom free and the control ultrasonography revealed the hemangiomatous area to be 3×2×3 cm. He was readmitted with gastrointestinal bleeding again when he was 18 months old. It appeared that the family had discontinued Propranolol 6 months ago as they thought their child was going well. The ultrasonography at this last admission revealed a 3×2×3 cm hemangiomatous area and after management of acute bleeding, Propranolol was restarted at a dose of 2 mg/kg/day. The patient was admitted for routine control 6 months later. The patient was asymptomatic with normal vital signs. The laboratory tests revealed K+: 6.5 mmol/L, (control: 8.2 mmol/L) with other biochemical tests to be normal. Propranolol was discontinued. He was hospitalised for hyperkalaemia, and hydration of 3000 cc/m2/day, alkalinisation, furosemide 2 mg/kg/day and 0.15 mg/kg/dose 6 doses/day inhaler salbutamol were started on the first day of hospitalisation. The patient was restricted for potassium containing diet as well. He was monitored for cardiac effects of hyperkalaemia. At the second week of his hospitalisation, K+ was found to be of 3.85 mmol/L and Propranolol was started again at a dose of 0.5 mg/kg/day.

**Author’s opinion:**
Hyperkalaemia has not been a known complication of Propranolol therapy since recently; however, as it induces apoptosis of cells in haemangioma, hyperkalaemia is attributed to the potassium content released by apoptotic haemangioma cells. The mechanism of Propranolol to cause hyperkalaemia has been reported to impair β-2 receptors interfering with potassium into the cells as renal potassium excretion remains intact.
Company’s position:
Hyperkalaemia is already considered as an important potential risks in case of large ulcerated hemangioma in the risk management plan of the European application dossier. No cases of hyperkalaemia have been reported during the clinical trials with V0400SB and the compassionate use program. No new signal has emerged from the analysis of this article.

-The second article (Jian et al.) presented one case of agranulocytosis among the adverse events reported in 97 patients treated with Propranolol 2 mg/kg/day in China. One case of agranulocytosis has been reported in an 11-month-old infant who was administered propranolol (2 mg/kg/d) for 3 weeks. The physical examination results were as follows: temperature, 38.6°C; HR, 138 beats/min; respiration, 40/min; throat redness; no enlargement of tonsils or lymphadenopathy; no coarse breath sounds; and no rales or wheezing. A routine blood test showed a WBC count of $2.8 \times 10^9$/L and a neutrophil count of $0.4 \times 10^9$/L. A bone marrow puncture and viral serologic test were performed to exclude primary or virus-associated agranulocytosis. Propranolol was discontinued and an anti-infective drug and granulocyte colony stimulating factor were administered for 1 month, after which the patient’s clinical symptoms disappeared, and the blood parameters returned to normal.

Author’s opinion:
Since there were no signs of infection and the clinical symptoms disappeared after discontinuation of Propranolol, the authors suggested that the agranulocytosis was associated with Propranolol treatment.
Company’s position:
In 1973, Nawabi reported a first case of agranulocytosis in an adult patient possibly linked to propranolol in the literature (Nawabi, 1973). This 64-year-old patient had a white blood cell count of 1400/mm$^3$ including 2% of neutrophils in the peripheral blood, with lymphocytes the remaining cells. Two days before, the patient had developed a sore throat, chills and fever that did not respond to erythromycin. Six weeks prior the onset of the illness and while on a maintenance regimen of procaïnamide, he was prescribed 10mg of propranolol hydrochloride, 4 times daily. The procaïnamide was discontinued 4 weeks before admission and the dosage of propranolol was increased progressively until 40mg 4 times daily. The medication had been maintained for 6 days and discontinued after the white blood cell count revealed agranulocytosis. He was hospitalized with fever 38.9°C and bone marrow aspirate revealed a complete absence of mature granulocytes. The temperature and the white blood cell returned to normal after 6 days of cephalothin and kanamycin. He recovered on 11th hospital day and bone marrow aspirate was normal. Additional studies were performed to clarify the etiologic role of propranolol or procaïnamide as a cause of agranulocytosis. The leukotoxin test was performed by exposing a known quantity of WBC in presence of complement for 30 or 60 minutes to aliquots of control and test sera with and without propranolol, and procainamide. In this patient, the lysis index was was 414 for propranolol and 3 for procaïnamide. The authors conclude that the development of propranolol-linked leukocyte agglutinins in the patient’s serum was responsible for the peripheral destruction of leucocytes. The patient was inadvertently rechallenged by the administration of procaine as a local anaesthetic for the second puncture without any side effects.

Additionally to these individual cases of agranulocytosis reported with propranolol, the risks of agranulocytosis (and aplastic anemia) in relation to the use of cardiovascular drugs were evaluated in a population-based case-control study conducted in Israel and Europe (total population, 23 million). Cardiovascular drug use in the week before onset of illness was compared between 270 patients hospitalized with agranulocytosis and 1870 hospitalized control subjects. Propranolol (relative risk, 2.5), was significantly associated with agranulocytosis.

During V0400 clinical trials, no case of agranulocytosis has been reported. Furthermore, no cases of agranulocytosis have been reported in patients below 20 years of age in the FDA safety data base.
Conclusion:
To conclude, agranulocytosis is considered as a non-important identified risk and is included in section 4.8 of the SmPC of Hemangiol with frequency unknown.

As for the results of the CUP, the profile of the reported ADRs during the use of Propranolol in the treatment of proliferative IH in an off-label context was very similar to the known safety profile of Propranolol in adults. Bradycardia, hypotension, hypoglycaemia and related seizure, and bronchospasm and bronchial hyperreactivity reactions were experienced by a small proportion of patients receiving oral Propranolol. Sleep disorders, diarrhoea, and cold extremities were the most frequent other non-serious ADRs reported.

No predisposing factors were identified for any ADR. No predominant time to onset was identified for any ADR except for hypotension, diarrhoea and cold extremities that mainly occurred within the first 5 days of treatment. Propranolol was usually considered well tolerated but full data on safety were usually not provided, except in some detailed case reports.

The analysis of the data from the publications during this period confirms the safety profile of propranolol established in the treatment of IH during the Pierre Fabre clinical trials and the CUP.
2.5. CLINICAL TRIALS

At the data lock point of this bridging report, all the trials with V00400SB were completed. Table 20 presents cumulatively all the trials performed with V0400SB.

Table 20: Clinical trials conducted by Pierre Fabre with V0400SB

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Phase</th>
<th>Study Title</th>
<th>Main Study Objective</th>
<th>Enrollment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>V00400 SB 1 01 2A</td>
<td>I</td>
<td>Evaluation of PK parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol formulation (tablet). A monocentric, randomized, open-label, single dose, 2-way crossover study.</td>
<td>To evaluate the PK parameters of V0400SB (solution) compared to the reference propranolol hydrochloride formulation (tablet) after a single oral dose in 12 healthy volunteers.</td>
<td>12 healthy volunteers</td>
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<tr>
<td>Studies conducted in infants with proliferating IH (target population)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V00400 SB 1 02</td>
<td>I</td>
<td>A multicenter, open-label, repeated dose, PK study of propranolol in infants treated for proliferating IH requiring systemic therapy.</td>
<td>To characterize the PK of V0400SB at steady-state in infants during a treatment for proliferating IH requiring systemic therapy.</td>
<td>23 infants with IH</td>
<td>Completed</td>
</tr>
<tr>
<td>V00400 SB 2 01</td>
<td>II/III</td>
<td>A randomized, double-blind, placebo-controlled, multiple-dose, multicenter, adaptive Phase II/III study in infants with proliferating IH requiring systemic therapy to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo.</td>
<td>To identify the appropriate dose and duration of V0400SB treatment and demonstrate its superiority over placebo based on the complete/nearly complete resolution of target IH at Week 24.</td>
<td>460 infants with IH</td>
<td>Follow-up until W96 completed.</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V00400 SB 3 01</td>
<td>III</td>
<td>Multicenter, open-label study of propranolol in infants with proliferating IH requiring systemic therapy.</td>
<td>To allow the use of V0400SB with adequate conditions of administration and follow up in infants requiring this systemic treatment after participation in a previous trial. The safety profile (including long-term impact) and the effect on the resolution of target proliferating IH were documented.</td>
<td>11 infants with IH</td>
<td>Completed</td>
</tr>
</tbody>
</table>

IH: infantile haemangioma; PK: pharmacokinetics.

On 08th March 2013, a marketing authorization application was submitted in Europe via Centralised Procedure for V0400SB. The European marketing authorisation was granted on 23rd April 2014 for Hemangiol 3.75 mg/mL, oral solution. A New Drug Application was submitted in the USA on 17th May 2013 and granted on 14th March 2014 under the tradename of HEMANGEOL™ (Propranolol hydrochloride) oral solution 4.28 mg/mL.
A marketing authorization for Hemangiol was also granted in Switzerland on 18th August 2014. Registrations process is also ongoing in Australia, Canada and Russia.

The following safety concerns of Hemangiol in the treatment of infantile IH have been identified:

| Important identified risks | ▪ Bradycardia  
|                           | ▪ Prolonged atrio-ventricular conduction or intensification of an AV block  
|                           | ▪ Hypotension  
|                           | ▪ Hypoglycaemia and related seizure  
|                           | ▪ Bronchospasm and bronchial hyperreactivity reactions  
| Important potential risks | ▪ Cerebrovascular complication in case of PHACE syndrome with SNC involvement  
|                           | ▪ Hyperkalaemia in case of large ulcerated IH  
|                           | ▪ Potential risk of administration error  
|                           | ▪ Drug interaction with anesthetic agents  
| Missing information       | ▪ Off-label use  
|                           | ▪ Long-term effects (including on growth)  
|                           | ▪ Drug interaction through breast-feeding  
|                           | ▪ Dosing and treatment of premature infants before the corrected age of at least 35 days  

Other identified risks (not considered as important according to the definition)
- Gastrointestinal disorders: diarrhoea
- Neurological disorders: sleep disorders with nightmares
- Psychiatric disorders: agitation, somnolence
- Vascular disorders : peripheral coldness, Raynaud’s syndrome
- Agranulocytosis
3. CONCLUSION CONCERNING THE RISK/BENEFIT RATIO FOR THE MEDICINAL PRODUCT IN THE CONTEXT OF THE CUP AND CONDITIONS FOR USE

Up to 31st July 2014, a total of 1661 infants have been treated in France in the Compassionate Use Program. In line with the indication: “proliferating IH which were life-threatening or gave rise to a functional risk, and ulcerating IH not responding to simple treatment”, functional impairment was reported in 72.4%, severe ulceration in 39.3% and vital risk in 15.8% of patients.

The safety profile of oral propranolol in the treatment of infants with infantile hemangioma was expected to be very similar to the safety profile in approved indications in adult, whatever the considered age group. This has been confirmed through the clinical development program, with V0400SB displaying a comparable safety profile to marketed propranolol products and no new safety signals arising either during or after treatment. These results are supported by data from the CUP and scientific literature.

The serious adverse drug reactions mainly concerned cardiac disorders (bradycardia, aggravation of atrio-ventricular conduction), vascular disorders (hypotension), respiratory disorders (bronchospasm and bronchial hyperreactivity reactions), and metabolic and nutritional disorders (hypoglycaemia, hypoglycaemic seizure).

The non-serious events mainly concerned sleep disorders (insomnia, somnolence, nightmares).

Pre-treatment evaluation, dose escalation, and monitoring procedures allowed an adequate minimization of cardiovascular and respiratory disorders at treatment initiation. Proper education of parents and caregivers must be maintained to prevent risk of hypoglycaemia and of aggravation of bronchial hyperreactivity reactions especially during winter time.

The information from the numerous scientific publications complete the knowledge about the risks related to the treatment of this population by propranolol.

On the basis of all the reviewed evidence, it may be concluded that Propranolol PFD, used in accordance with the specific conditions described in the SPC, is an effective and well-tolerated treatment for infantile haemangioma requiring systemic therapy.
LITERATURE REFERENCES

Diarrhea associated with propranolol treatment for hemangioma of infancy  

Treatment of periocular infantile hemangiomas with propranolol: case series of 18 children  
Ophthalmology 2011 Jun;118(6):1184-8

Bagazgoitia I, Torrelo A, Lopez-Gutierrez JC et al.  
Propranolol for infantile hemangiomas  

Propranolol in the management of infantile hemangiomas: clinical response and predictors  

Begaud B, Evreux JC, Jouglard J, Lagier G  
Unexpected or Toxic Drug reaction Assessment (imputation)  
Therapies 1985;40:111-8

Belen B, Oguz A, Okur A, Dalgic B.  
A complication to be aware of: hyperkalaemia following propranolol therapy for an infant with intestinal haemangiomatosis.  

Propranolol for the treatment of severe hemangiomas of infancy: results from a series of 28 patients  
Actas Dermosifiliogr. 2011 Sep;102(7):510-6

Bertrand J, McCuaig C, Dubois J, et al.  
Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study  

Propranolol in the treatment of problematic infantile hemangioma: review of 35 consecutive patients from a vascular anomalies clinic  

Outpatient treatment of infantile hemangiomas with propranolol: a prospective study  
Actas Dermosifiliogr. 2012 Nov;103(9):806-15

Blatt J, Morrell DS, Buck S, et al.  
B-blockers for infantile hemangiomas: a single-institution experience  

Bonifazi E, Acquafredda A, Milano A, et al  
Severe hypoglycaemia during successful treatment of diffuse hemangiomatosis with propranolol  

Bossemani T, Puttgen KB, Huisman TA, Tekes A  
Multifocal infantile hepatic hemangiomas - imaging strategy and response to treatment after propranolol and steroids including review of the literature  

Breur JM, de Graaf M, Breugem CC, Pasmans SG  
Hypoglycaemia as a result of propranolol during treatment of infantile hemangioma: a case report  

Broeks L.J., Hermans D.J.J., Dassell A.C.M., Van der Vleuten C.J.M., Van Beynum I.M.  
Propranolol treatment in life-threatening airway hemangiomas: A case series and review of literature  

Propranolol for infantile hemangiomas: early experience at a tertiary vascular anomalies center  
Laryngoscope 2010 Apr;120(4):676-81

Tumor lysis syndrome after propranolol therapy in ulcerative infantile hemangioma: rare complication or incidental finding?  
Dermatology 2012;224(2):106-109

Chai Q, Chen WL, Huang ZQ, et al.  
Preliminary experiences in treating infantile hemangioma with propranolol
Ann Plast Surg. 2011;1-4
Chang LC, Haggstrom AN, Drolet BA, et al.
Growth characteristics of infantile hemangiomas: implications for management
Pediatrics. 2008 Aug;122(2):360-7
Chik KK, Luk CK, Chan HB, Tan HY
Use of propranolol in infantile haemangioma among Chinese children
Hong Kong Med J. 2010;16(5):341-6
Clark DJ, Chan KC, Gibbs JL
Propranolol induced bradycardia in tetralogy of Fallot
Br Heart J. 1989 Apr;61(4):378-379
Corapcioglu F, Büyükkapu-Bay S, Binnetoglu K, et al.
Preliminary results of propranolol treatment for patients with infantile hemangioma
D’Angelo G, Lee H and Weiner RI
cAMP-dependent protein kinase inhibits the mitogenic action of vascular endothelial growth factor and fibroblast growth factor in capillary endothelial cells by blocking Raf activation
J Cell Biochem. 1997 Dec1;67(3):353-366
De Graaf M, Breur J, Raphaël MF, et al.
Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants
Don-Wauchope AC, et al.
Pediatric critical values: laboratory-pediatrician discourse
Clin Biochem. 2009 Nov;42(16-17):1658-61
Moshe Dotan, Avraham Lorber.
Congestive heart failure with diffuse neonatal hemangiomatosis – case report and literature review.
Acta Paediatr 2013 102(5) e232-8
Drolet BA, Frommelt PC, Chamlin SL, et al.
Initiation and use of propranolol for infantile hemangima: report of a consensus conference
Pediatrics 2013 Jan;131(1):128-140
Dyme JL, Thampan A, Han EJ, et al.
Propranolol for infantile haemangiomas: initiating treatment on an outpatient basis
Cardiol Young. 2012 Aug;22(4):424-9
El-Essawy R, Galal R, Abdelbaki S
Non selective beta-blocker propranolol for orbital and periorbital hemangiomas in infants: a new first-line of treatment?
Clin Ophthalmoology 2011;5(5):1639-44
Propranolol for infantile hemangiomas: a preliminary report on efficacy and safety in very low birth weight infants
Fode B, Wömper M, Jedwialyttes S, Rebmann H
Hypoglykämischer krampfanfall unter propranolol
Monatsschr Kinderheilkd 2010;158(7):677-8
Fuchsmann C, Quintal MC, Giguere C, et al.
Propranolol as first-line treatment of head and neck hemangiomas.
Propranolol for infantile haemangiomas and neuroglycopenic seizures
Acta Paediatr. 2010 Dec;99(12):1756
Frost G., Relic J.
Dangers of propranolol in preterm infants
Australas. J. Dermatol. 2013 54:3 (237-238)
Genzen JR and Tormey CA for the Education Committee of the Academy of Clinical Laboratory Physicians and Scientists
Pathology consultation on reporting of critical values
Propranolol treatment for severe infantile hemangiomas: a single-centre 3-year experience
Dental caries as a side effect of infantile hemangioma treatment with propranolol solution
CONFIDENTIAL
Haider KM, Plager DA, Neely DE, et al.
*Outpatient treatment of periorcular infantile hemangiomas with oral propranolol*

Harper J
*Propranolol for infantile haemangiomas: experience from Great Ormond Street Hospital*
Hong Kong J Dermatol Venereol; 2011;19:37-38

Hasan M, et al.
*Propranolol for hemangiomas.*
Pediatr Surg Int 2013 29(3) 257-62

*Propranolol, a very promising treatment for ulceration in infantile hemangiomas: a study of 20 cases with matched historical controls*

Hogeling M, Adams S, Wargon O
*A randomized controlled trial of propranolol for infantile hemangiomas*
Pediatrics 2011;128(2):e259-e266

Holland KE, Frieden IJ, Frommelt PC, et al.
*Hypoglycaemia in children taking propranolol for the treatment of infantile hemangioma*
Arch Dermatol. 2010 Jul;146(7):775-778

Holmes WJM, Mishra A, Gorst C, Liew SH
*Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas*

Hsu TC, Wang JD, Chen CH, et al.
*Treatment with propranolol for infantile hemangioma in 13 Taiwanese newborns and young infants*

JannMohamed SR, de Laat PCJ, Madern GC, Oranje AP
*Do we have to check glucose in patients with haemangioma of infancy treated with beta-blockers?*

Javia LR, Zur KB, Jacobs IN
*Evolving treatment in the management of laryngotracheal hemangiomas: will propranolol supplant steroids and surgery?*

Li J., Jian D., Chen X., Babajee K., Su J., Li J., Hu X., Xie H
*Adverse effects of propranolol treatment for infantile hemangiomas in China*

Koay AC, Choo MM, Nathan AM, et al.
*Combined low-dose oral propranolol and oral prednisolone as first-line treatment in periorcular hemangiomas*

Kost GJ
*Critical limits for emergency clinician notification at United States children’s hospitals*
Pediatrics 1991 Sep;88:597-603

Küpeli S
*Use of propranolol for infantile hemangiomas*
Pediatr Hematol Oncol. 2012 Apr;29(3):293-8

Lawley LP, Siegfried E and Todd JL
*Propranolol treatment for hemangiomia of infancy: risks and recommendations*

Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al.
*Propranolol for severe hemangiomas of infancy*

*Propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma: a preliminary retrospective study of Frecon experience*

Lv MM, Fan XD, Su LX
*Propranolol for problematic head and neck hemangiomas: an analysis of 37 consecutive patients*
Int J Pediatr Otorhinolaryngol. 2012 Apr;76(4):574-578
Malik M.A., Menon P., Rao K.L.N., Samujh R.
*Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: A randomized controlled study*

*Propranolol for complicated infantile haemangiomas: a case series of 30 infants*  
Br J Dermatol. 2010 Feb 1;162(2):466-8

*Massive response of severe infantile hepatic hemangioma to propranolol*  
Peditr Blood Cancer 2010 Jan;54(1):176

Mathers LH and Frankel LR
*Pediatric Emergencies and Resuscitation*  

*Propranolol use in PHACE syndrome with cervical and intracranial arterial anomalies: collective experience in 32 infants*  

Missoi TG, Lueder GT, Gilbertson K, Bayliss S  
*Oral propranolol for management of periorcular infantile hemangioma*  
Arch Ophthalmol. 2011 Jul;129(7):899-903

Newman TJ, Virning NL, Pakshi R, Athinarayanan PR  
*Complications of propranolol use in neonatal thyrotoxicosis*  

Ozyoruk D., Zengin E.
*Propranolol treatment of complicated hemangiomas*  
Indian journal of pediatrics (2014) 81:4 (368-370)

Paterlini A, Salmi A, Buffoli F, Lombarodi C  
*Heart failure and endoscopic sclerotherapy of variceal bleeding*  
Lancet. 1984 Jun2;1(8388):1241

Pavlakovic H, Kietz S, Lauerer P et al.  
*Hyperkalaemia complicating propranolol treatment of an infantile hemangioma*  
Pediatrics 2010 Dec;126(6):e1589-93

Phillips RJ, Penington AJ, Bekhor PS and Crock CM  
*Use of propranolol for treatment of infantile haemangiomas in an outpatient setting*  

*Propranolol vs corticosteroids for infantile hemangiomias: a multicenter retrospective analysis*  
Arch Dermatol. 2011 Dec; 147(12):1371-6

Rosse KW, Suh KY, Meyer AK et al.  
*Propranolol in the management of airway infantile hemangiomas*  

*Propranolol for treatment of ulcerated infantile hemangiomas*  
J Am Acad Dermatol. 2011 May;64(5):827-32

Sanchez-Carpintero I, Ruiz-Rodriguez R and Lopez-Gutierrez JC  
*Propranolol en hemangiomas infantiles: eficacia clinica, riesgos y recomendaciones*  
Actas Dermo-Sifiliograficas. 2011 Dec;102(10):766-79

Sans V, Dumas de la Roque E, Berge J, et al.  
*Propranolol for severe infantile hemangiomas: follow-up report*  
Pediatries. 2009 Sep;124(3);e423-31

Santos S, Torrelo A, Tamariz-Martel A and Dominguez MJ  
*Clinical observations on propranolol use for paediatric airway haemangiomas*  

Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas  

Schupp CJ, Kleber JB, Günther P and Holland-Cunz S  
*Propranolol therapy in 55 infants with infantile hemangioma: dosage, duration, adverse effects and outcome*  
Shepherd D, Adams S, Wargon O and Jaffe A
Chilhood wheeze while taking propranolol for treatment of infantile hemangiomas

Siparsky G, Accurso FJ
Chemistry and haematology reference intervals
Current Diagnosis and Treatment, Hay et al. ed., 2011;chapter45:1311-18

Snir M, Reich U, Siegel R, et al.
Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol
Eye 2011 Dec;25(12):1627-34

Tan ST, Itinteang and Leadbitter P
Low-dose propranolol for multiple and cutaneous hemangiomas with deranged liver function
Pediatrics 2011 b Mar;127(3):772-e776

Tan ST, Itinteang T and Leadbitter P
Low-dose propranolol for infantile haemangioma
J Plast Reconstr Aesthet Surg. 2011 a Mar;64(3):292-300

Thoumazet F, Léauté-Labrèze C, Colin J, Mortemousque B
Efficacy of systemic propranolol for severe infantile hemangioma of the orbit and eyelid: a case study of eight patients

Yuan S.-M., Cui L., Guo Y., Xue C.-Y., Hong Z.-J., Jiang H.-Q.
Management of periorbital hemangioma by intralesional glucocorticoids and systemic propranolol: A single-center retrospective study

Oral propranolol for treating infantile hemangiomas: a case series of 57 patients
Actas Dermosifiliogr. 2012 Oct;103(8):708-17

Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study
Pediatric Dermatology 2011 Mar-Apr;28(2):94-98
4. *Complete extracted safety data for the selected literature*
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haider et al.[2010]USA</td>
<td>17</td>
<td>Bsl: ECG</td>
<td>Monitoring BP/HR 24h after any dosage change</td>
<td>No DA or DD</td>
<td>No hypotension, no bradycardia</td>
<td>No symptomatic hypoglycemia</td>
<td>6</td>
<td>35,3%</td>
<td>Gastrointestinal upset (mild, transient)</td>
<td>Abdominal discomfort</td>
<td>2</td>
<td>11.76%</td>
<td>ND</td>
</tr>
<tr>
<td>Metry et al.[2013]USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td>Gastrointestinal upset</td>
<td>Abdominal discomfort</td>
<td>1</td>
<td>3,13%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>Betlloch-Mas et al.[2012]Spain</td>
<td>20</td>
<td>ECG and echo, BP, HR, lab at bsl</td>
<td>BP, HR, BG, weight: 5h after 1st dose then twice monthly/1st month, then monthly</td>
<td>No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty</td>
<td>30,0%</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>1</td>
<td>5,00%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Balma-Mena[2012]Canada</td>
<td>44</td>
<td>ECG, BP, HR, BG: bsl, every 2 weeks for 1st month then monthly</td>
<td>All events minor</td>
<td>31,8%</td>
<td>Behavioural changes</td>
<td>Abnormal behaviour</td>
<td>3</td>
<td>6,82%</td>
<td>ND</td>
<td>3</td>
<td>None</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Lao[2014]China</td>
<td>635</td>
<td>Hosp 3-4 days</td>
<td>&quot;No significant/serious AEs&quot;</td>
<td>1/24 stopping for side effect</td>
<td>3,8%</td>
<td>No weight gain</td>
<td>Abnormal weight gain</td>
<td>3</td>
<td>0,47%</td>
<td>ND</td>
<td>ND</td>
<td>3 Resolution after tt disc</td>
<td></td>
</tr>
<tr>
<td>Hasan[2013]Bangladesh</td>
<td>36</td>
<td>BP HR for first 3h</td>
<td>Monthly FU</td>
<td>No major change in HR, no change in BP</td>
<td>0,0%</td>
<td>ND</td>
<td>Acute renal failure</td>
<td>(following diarrhea in a patient admitted 2.5 months before for respiratory distress)</td>
<td>Acute kidney injury</td>
<td>1</td>
<td>2,78%</td>
<td>Between 2 months and 2.5 months after treatment initiation</td>
<td>ND</td>
</tr>
<tr>
<td>Andersen[2014]Denemark</td>
<td>37</td>
<td>Monitoring 1-2 D: BP, HR, BG</td>
<td>Echocardiography&lt;3months</td>
<td>FU: W2 then 1 to 2 month-interval</td>
<td>32,4%</td>
<td>Agitation (mild)</td>
<td>Agitation</td>
<td>4</td>
<td>10,81%</td>
<td>ND</td>
<td>ND</td>
<td>Resolved after cessation of tt</td>
<td></td>
</tr>
<tr>
<td>Sans et al.[2009]France</td>
<td>32</td>
<td>ECG, echocardiography</td>
<td>Short hosp 24h</td>
<td>Monitoring BP HR every h over 6 first h of tt</td>
<td>Evaluation after 10 days then monthly</td>
<td>Mild side effects</td>
<td>0,0%</td>
<td>ND</td>
<td>Agitation</td>
<td>Agitation</td>
<td>2</td>
<td>6,25%</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Abdominal discomfort Total**: 3 (0,08%)

**Abdominal pain Total**: 1 (0,03%)

**Abnormal behaviour Total**: 3 (0,08%)

**Abnormal weight gain Total**: 3 (0,08%)

**Acute kidney injury Total**: 1 (0,03%)

**Agitation Total**: 6 (0,16%)
<table>
<thead>
<tr>
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<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jian</td>
<td>2014</td>
<td>China</td>
<td>97</td>
<td>Lab tests</td>
<td>ECG BP HR monitoring 48h after 1st dose</td>
<td>Hosp for 3-5 days</td>
<td>Monthly FU</td>
<td>0,0%</td>
<td>Agranulocytosis (neutropenia)</td>
<td>WB: 2.8<em>10^9/L, Neutro: 0,4</em>10^9/L, Temp: 38°6 WO infection</td>
<td>Agranulocytosis</td>
<td>1</td>
<td>1,03%</td>
<td>3 weeks DD</td>
</tr>
<tr>
<td>Schiestl</td>
<td>2011</td>
<td>Switzerland</td>
<td>25</td>
<td>ECG, echocardo, HR, BP</td>
<td>2-3-day in-patient observation at initiation</td>
<td>Monitoring 1h after adm of each dose: HR BP and continuous HR monitoring during sleep</td>
<td>After complete D2: ECG</td>
<td>FU after 1 week, 1 month and every 2 months (clin HR BP)</td>
<td>No relevant hemodynamic changes</td>
<td>No ti Drop out</td>
<td>No hypoglycemia but BG not routinely measured</td>
<td>0,0%</td>
<td>Agranulocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Laforgia</td>
<td>2009</td>
<td>Italy</td>
<td>23</td>
<td>1-day hosp</td>
<td>Monitoring (BP, HR, BG) on D1</td>
<td>FU monthly, CBG every 10-15 d</td>
<td>[No symptomatic decrease of HR or BP]</td>
<td>3</td>
<td>13,0%</td>
<td>Severe bronchospasm during asthmatic bronchitis</td>
<td>Asthma</td>
<td>1</td>
<td>4,35%</td>
<td>2.5 months DD</td>
</tr>
<tr>
<td>Leboulanger et al.</td>
<td>2010</td>
<td>France</td>
<td>14</td>
<td>ND</td>
<td>3</td>
<td>21,4%</td>
<td>Asthma, severe</td>
<td>3</td>
<td>13,0%</td>
<td>Wheeze (related to underlying allergic asthma)</td>
<td>Asthma</td>
<td>1</td>
<td>3,13%</td>
<td>3 months DD</td>
</tr>
<tr>
<td>Sans et al.</td>
<td>2009</td>
<td>France</td>
<td>32</td>
<td>ECG, echocardio</td>
<td>Short hosp 24h</td>
<td>Monitoring BP HR every h over 6 first h of ttt Evaluation after 10 days then monthly</td>
<td>[Mild side effects]</td>
<td>0,0%</td>
<td>ND</td>
<td>Wheeze (related to underlying allergic asthma)</td>
<td>Asthma</td>
<td>1</td>
<td>3,13%</td>
<td>3 months DD</td>
</tr>
<tr>
<td>Schupp</td>
<td>2011</td>
<td>Germany</td>
<td>55</td>
<td>ECG, echocardio</td>
<td>Initial monitoring of VSI</td>
<td>2 night in-patient hosp</td>
<td>BG not checked</td>
<td>FU after 2 and 4 weeks then monthly (inc BP HR)</td>
<td>[No hypotension, no bradycardia, no symptomatic hypoglycemia]</td>
<td>No severe AEs</td>
<td>13</td>
<td>23,6%</td>
<td>Bronchial asthma (temporary aggravation of preexisting asthma)</td>
<td>Asthma</td>
</tr>
<tr>
<td>Xiao</td>
<td>2013</td>
<td>China</td>
<td>64</td>
<td>Hosp first 3 days</td>
<td>Bsl ECG</td>
<td>Discontinuation if serious cough with dyspnea</td>
<td>FU monthly: BP HR BG</td>
<td>No severe AE</td>
<td>12/13 pts with mild AEs and discontinuation</td>
<td>13</td>
<td>20,3%</td>
<td>Asthma aggravation &quot;temporary aggravation of pre-existing bronchial asthma&quot; &quot;bronchial hyper-reactivity during viral infection&quot;</td>
<td>Asthma</td>
<td>1</td>
</tr>
</tbody>
</table>

**AE Total**: 5 (0,13%)
<table>
<thead>
<tr>
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<th>Year</th>
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<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE (%)</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE (%)</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogeling</td>
<td>2011</td>
<td>Australia</td>
<td>19</td>
<td>Basl ECG, echocarido, lab [Monitoring BP HR BG at each visit every 4 weeks]&lt;6 months hosp for first dose at W1 and W2; AE monthly][Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7][No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>Elevated Alkaline Phosph. Level (transient)</td>
<td>Blood alkaline phosphatase increased</td>
<td>1</td>
<td>5.26%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Baumun</td>
<td>2014</td>
<td>USA</td>
<td>10</td>
<td>Basl ECG and VS][BP, HR, BG 1 hr after each dose for the first 3 doses][Premature stop of study owing to severe AEs in 0 pts on propranolol vs 6/8 pts on prednisolone][0 DD for AE on propranolol versus 5 DD for AE on prednisolone][32 AEs on propranolol vs 44 on prednisolone][Severe (CTCAE grade 3) AEs : in 1 patient on propranolol vs 11 in 5 patients on prednisolone (9 decline in growth or weight, 1 adrenal crisis + viral gastro-enteritis, 1 severe dehydration warranting hospt)][Severe growth retardation in 0 patients/propranolol vs 5 on prednisolone</td>
<td>9</td>
<td>90,0%</td>
<td>9 (90%)</td>
<td></td>
<td></td>
<td>Asymptomatic BP decrease[3AEs on prednisolone</td>
<td>Blood pressure decreased</td>
<td>1</td>
</tr>
<tr>
<td>El-Essawy</td>
<td>2011</td>
<td>Egypt</td>
<td>15</td>
<td>Hosp 1-2 weeks][Basl: BP, BG, electrolytes][FU: every 2 wks during the first 3 months then monthly][No SAE][Acceptable decrease in HR and BP during the 1st month in all patients</td>
<td>2</td>
<td>13,3%</td>
<td>“Acceptable” decrease in BP</td>
<td>Blood pressure decreased</td>
<td>15</td>
<td>100,0%</td>
<td>Within the 1st month</td>
<td>None</td>
</tr>
<tr>
<td>Erbay</td>
<td>2010</td>
<td>Turkey</td>
<td>16</td>
<td>Hosp for &lt; 3 months of age][Others over 8h][HR, BP hourly][Cs cardiped][Lab][Then outpatient if no AE][FU: 10 days then monthly][No DD][AE][No hypoglycemia, diarrhea, wheezing, agitation, cold arms</td>
<td>0,0%</td>
<td>ND</td>
<td>Decreased BP and HR (no bradycardia or hypotension)</td>
<td>Blood pressure decreased</td>
<td>2</td>
<td>12,5%</td>
<td>Within the first 6h of tit</td>
<td>None (monitoring 24h, stimulation)</td>
</tr>
<tr>
<td>Jian</td>
<td>2014</td>
<td>China</td>
<td>97</td>
<td>Lab test][ECG BP HR monitoring 48h after 1st dose][Hosp for 3-5 days][Monthly FU</td>
<td>0,0%</td>
<td></td>
<td>Cyanosis and cold extremities + HR/BP decreased 118, =&gt;80 bpm, 105/87 =&gt; 90/65 mmHg][SPO2 97-99=&gt;80-85, ECG normal</td>
<td>Blood pressure decreased</td>
<td>1</td>
<td>1,0%</td>
<td>10 minutes after the second dose of propranolol</td>
<td>Oxygenotherapy 3 min][DD</td>
</tr>
<tr>
<td>Katona</td>
<td>2012</td>
<td>Hungary</td>
<td>22</td>
<td>Prent Clin exam][ECG BG first 48h][BP HR BG at all controls</td>
<td>2</td>
<td>9,1%</td>
<td>Lower blood pressure</td>
<td>Blood pressure decreased</td>
<td>2</td>
<td>9,1%</td>
<td>ND</td>
<td>Dose reduced to 1 mg/kg/day for 2 weeks</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
</tr>
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<tr>
<td>Ma</td>
<td>2013</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days [Bsl HR, SBP, DBP, SaO2, ECG, standard lab] Every 3 h: clin, [ECG monitoring for first 3 days]HR BP 1 h after each dose [FU with ASAT, ALAT, thyroid function and BG] Every 3 months</td>
<td>[Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycemia] [Slight decrease HR BP] [No bronchospasms or leukocytosis]</td>
<td>0,0%</td>
<td>Slight decrease in BP</td>
<td>Blood pressure decreased</td>
<td>89</td>
<td>100,0%</td>
<td>Within 7 days</td>
<td>None</td>
</tr>
<tr>
<td>Meng</td>
<td>2012</td>
<td>China</td>
<td>22</td>
<td>Hosp 1 week [HRE BP 1, 3, 6h after propranolol use, lab, cardiac US, BG 3, 7, 14, 28 days after propranolol use then monthly]</td>
<td>BP slightly decreased</td>
<td>Blood pressure decreased</td>
<td>5</td>
<td>22,7%</td>
<td>Within first 2 weeks</td>
<td>ND</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Sans et al.</td>
<td>2009</td>
<td>France</td>
<td>32</td>
<td>ECG, echocardiogram [Short hosp 24h] Monitoring BP HR every h over 6 first h of ttt Evaluation after 10 days then monthly</td>
<td>Mild side effects</td>
<td>0,0%</td>
<td>ND</td>
<td>Blood pressure decreased: 62/25 mmHg</td>
<td>Blood pressure decreased</td>
<td>1</td>
<td>3,1%</td>
<td>3 hours after ttt start (while sleeping)</td>
</tr>
<tr>
<td>Yuan</td>
<td>2013</td>
<td>China</td>
<td>35</td>
<td>Hosp 3 to 5 days [Bsl lab, chest RX, ECG] No disc for AE [All AEs are mild]</td>
<td>MILD GI reactions</td>
<td>No hypoglycemia or bronchospasm</td>
<td>35</td>
<td>100,0%</td>
<td>Blood pressure decreased</td>
<td>35</td>
<td>100,0%</td>
<td>ND</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts) Tt started at home Day care sitting at the target dose start [FU every 6 weeks]</td>
<td>62,1%</td>
<td>Lowered BP</td>
<td>Blood pressure decreased</td>
<td>5</td>
<td>2,9%</td>
<td>4/5 First 3 days</td>
<td>5 DA: dose reduction</td>
<td>Resolved</td>
</tr>
<tr>
<td>Georgountzou et al.</td>
<td>2012</td>
<td>Greece</td>
<td>28</td>
<td>Bsl HR, BP, BG, echocardiogram, ECG[H]R, BP, BG</td>
<td>During 1st 24h Hosp [HR, BP, every h for 6h post each dose; BG 1 h post-dose] [Then at W1 then monthly] [No documented bradycardia or hypoglycemia, no GI disturbance, behavioural change, sleep disturbance, or rash]</td>
<td>17,9%</td>
<td>Low DBP</td>
<td>Blood pressure diastolic decreased</td>
<td>1</td>
<td>3,57%</td>
<td>At onset of ttt</td>
<td>None, hospitalization</td>
</tr>
<tr>
<td>Georgountzou et al.</td>
<td>2012</td>
<td>Greece</td>
<td>28</td>
<td>Bsl HR, BP, BG, echocardiogram, ECG[H]R, BP, BG</td>
<td>During 1st 24h Hosp [HR, BP, every h for 6h post each dose; BG 1 h post-dose] [Then at W1 then monthly] [No documented bradycardia or hypoglycemia, no GI disturbance, behavioural change, sleep disturbance, or rash]</td>
<td>17,9%</td>
<td>Low SBP/DBP</td>
<td>Blood pressure systolic decreased</td>
<td>1</td>
<td>3,57%</td>
<td>1st day, 2h post each dose</td>
<td>DA: Dose reduced to 1.5 mg/kg/day and raised again to 2 mg/kg/day</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
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<tr>
<td>Manunza</td>
<td>2010</td>
<td>UK</td>
<td>30</td>
<td>Init at hosp</td>
<td>Bsl: full blood count, BG, echocard, abdo US, ECG</td>
<td>Monitor. for 4h at hosp after 1st dose and 1 week later : HR BP every 30 min</td>
<td>HR BP twice weekly for first 2 weeks then once weekly then monthly visit</td>
<td>No signif. ADR</td>
<td>Isolated SBP &lt;70 mmHg, asymptomatic</td>
<td>Blood pressure systolic decreased</td>
<td>3</td>
<td>10.00%</td>
</tr>
<tr>
<td>Jian</td>
<td>2014</td>
<td>China</td>
<td>97</td>
<td>Lab tests</td>
<td>ECG BP HR monitoring 48h after 1st dose</td>
<td>Hosp for 3-5 days</td>
<td>Monthly FU</td>
<td>0.0%</td>
<td>Body temperature decreased, low</td>
<td>Body temperature decreased</td>
<td>1</td>
<td>1.03%</td>
</tr>
<tr>
<td>Bertrand</td>
<td>2012</td>
<td>Canada</td>
<td>35</td>
<td>Bsl ECG and echo</td>
<td>BP, HR ambulatory monitor: first 4 to 6 weeks</td>
<td>FU: weekly first 4-6 weeks then twice a month</td>
<td>No SAE</td>
<td>All AEs at low dose (&lt;2mg/kg)</td>
<td>No symptom. hypoglycemia</td>
<td>Bradycardia (solitary episode of an awake HR of 55 bpm)</td>
<td>Bradycardia</td>
<td>1</td>
</tr>
<tr>
<td>Blatt et al.</td>
<td>2011</td>
<td>USA</td>
<td>54</td>
<td>Bsl: ECG (if less than 3 months of age)</td>
<td>[2 infants max dose: 4 or 5 mg/kg/d]</td>
<td>AEs moderate to severe</td>
<td>[5 AEs potentially life-threatening]</td>
<td>0.0%</td>
<td>ND</td>
<td>Bradycardia (transient heart rate 80)</td>
<td>Bradycardia</td>
<td>1</td>
</tr>
<tr>
<td>Blatt et al.</td>
<td>2011</td>
<td>USA</td>
<td>54</td>
<td>Bsl: ECG (if less than 3 months of age)</td>
<td>[2 infants max dose: 4 or 5 mg/kg/d]</td>
<td>AEs moderate to severe</td>
<td>[5 AEs potentially life-threatening]</td>
<td>16.7%</td>
<td>ND</td>
<td>Bradycardia, severe, potentially life-threatening</td>
<td>Bradycardia</td>
<td>1</td>
</tr>
<tr>
<td>Dyme</td>
<td>2012</td>
<td>USA</td>
<td>15</td>
<td>Outpatient</td>
<td>h of observation after 1st dose</td>
<td>FU cardio at W2 and every 1-2 months</td>
<td>No hypotension, hypoglycemia, bronchospasm, CS bradycardia</td>
<td>No complications at initiation</td>
<td>Mild decrease in HR continued throughout the 6-month FU period</td>
<td>Peak effect on HR at 5H after 1st dose, on DBP at 1H</td>
<td>0.0%</td>
<td>ND</td>
</tr>
<tr>
<td>El Ezzi</td>
<td>2014</td>
<td>Switzerland</td>
<td>29</td>
<td>Hospital 48H</td>
<td>Monitoring 2 days – hospital, start tt: cardiac ultrasound + ECG, blood glucose level and renal function</td>
<td>BP HR every 30 min for 4 h</td>
<td>FU: W1, W4 then every 8 weeks (HR BP)</td>
<td>If 0 severe ADR</td>
<td>No AE after 2nd dose</td>
<td>Transient bradycardia</td>
<td>Bradycardia</td>
<td>2</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients</td>
<td>Patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE MedDRA preferred term</td>
<td></td>
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<tr>
<td>Liu [2013] USA</td>
<td>2013</td>
<td>USA</td>
<td>31</td>
<td>0,0%</td>
<td>ND</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Luo [2014] China</td>
<td>2014</td>
<td>China</td>
<td>635</td>
<td>3,8%</td>
<td>24</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>McGee [2013] Ireland, UK</td>
<td>2013</td>
<td>Ireland, UK</td>
<td>24</td>
<td>16,7%</td>
<td>4</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missoi et al. [2011] USA</td>
<td>2011</td>
<td>USA</td>
<td>17</td>
<td>0,0%</td>
<td>50</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puttgen [2013] USA</td>
<td>2013</td>
<td>USA</td>
<td>50</td>
<td>100,0%</td>
<td>50</td>
<td>Asymptomatic bradycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiestl [2011] Switzerland</td>
<td>2011</td>
<td>Switzerland</td>
<td>25</td>
<td>0,0%</td>
<td>4</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments**

- **Liu [2013] USA**
  - 24h hosp [HR BP BG 3 and 1h and 3h before/after each dose of propralol] on average decrease by: [HR: 5 bpm] [SBP: 4 mmHg] [DBP or BG: no stat sign change] (Only HR sign attenuation over the first 3 doses) Conclusion: 24h hosp for hemodynamic monitoring not necessary for safe initiation [No SAE]
  - Bradycardia

- **Luo [2014] China**
  - Bradycardia

- **McGee [2013] Ireland, UK**
  - Bradycardia

- **Missoi et al. [2011] USA**
  - Bradycardia

- **Puttgen [2013] USA**
  - Bradycardia

- **Schiestl [2011] Switzerland**
  - Bradycardia
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiao[2013]China</td>
<td>64</td>
<td>Hosp first 3 days</td>
<td>[Bsl ECG][Discontinuation if serious cough with dyspnea][FU monthly: BP HR BG][No severe AE][12/13 pts with mild AEs and discontinuation]</td>
<td>13</td>
<td>20,3%</td>
<td>Bradycardia, mild</td>
<td>Bradycardia</td>
<td>1</td>
<td>1,56%</td>
<td>ND</td>
<td>1 None, symptomatic tt ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Corapcioglu et al.[2011]Turkey</td>
<td>12</td>
<td>Hosp for 3 days</td>
<td>[VS, BP, BG 1h after each dose][ECG daily][Then ECG, BP, BG every 2-4 weeks][Echocardioc at bsl and monthly][No hypoglycemia]</td>
<td>1</td>
<td>8,3%</td>
<td>Bradycardia (heart rate at 80 bpm, asymptomatic), transient</td>
<td>Bradycardia</td>
<td>1</td>
<td>8,33%</td>
<td>2-3 h of ttt start</td>
<td>None</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Park[2014]Korea</td>
<td>83</td>
<td>Bsl: Phys and lab exam, ECG, echocardioc</td>
<td>3-day monitoring: BP HR RR and BG</td>
<td>8</td>
<td>9.6%</td>
<td>Mild bradycardia</td>
<td>Bradycardia</td>
<td>1</td>
<td>1.20%</td>
<td>Within the first week of treatment</td>
<td>1 Treatment temporary discontinued then restarted at lower doses or delayed dose escalation (negative rechallenge)</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Bagazgoitia et al.[2011]Spain</td>
<td>Agentina</td>
<td>71</td>
<td>Cardio exam (EKG, BP, HR) before and BP, HR: 1 to 3 times a day during the 1st 2 or 3 days. 1 to 4 weeks later: EKG, BP, HR, BG in 10 cases 3 times a day during the 1st 3 days. Monthly FU</td>
<td>No hypotension, no hypoglycemia</td>
<td>Mean max -7/-10 mmHg</td>
<td>HR: -18 bpm</td>
<td>0,0%</td>
<td>ND</td>
<td>Cyanotic breath-holding spells</td>
<td>Breath holding</td>
<td>1</td>
<td>1.41%</td>
<td>ND</td>
</tr>
<tr>
<td>Hermans[2013]Netherlands</td>
<td>174</td>
<td>Prett ECG (all pts) Echocardioc (75 first pts)</td>
<td>Tt started at home</td>
<td>Day care sitting at the target dose start</td>
<td>FU every 6 weeks</td>
<td>108</td>
<td>62,1%</td>
<td>Breath holding spells</td>
<td>Breath holding</td>
<td>2</td>
<td>1.15%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Graaf (de) et al.[2011]Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>[Bsl: ECG][Outpatient FU: 1, 2, 4, 8, 12 weeks][BP, HR]</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Bronchial hyperreactivity</td>
<td>1</td>
<td>3,57%</td>
<td>After initiation of ttt</td>
<td>DD</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Graaf (de) et al.[2011]Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>[Bsl: ECG][Outpatient FU: 1, 2, 4, 8, 12 weeks][BP, HR]</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Bronchial hyperreactivity</td>
<td>2</td>
<td>7,14%</td>
<td>2 After initiation of ttt</td>
<td>2 TD</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
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<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Jian</td>
<td>2014</td>
<td>China</td>
<td>97</td>
<td>Lab tests</td>
<td>ECG BP HR monitoring 48h after 1st dose</td>
<td>Hosp for 3-5 days</td>
<td>Monthly FU</td>
<td>0,0%</td>
<td>Bronchial hyperreactivity(n o history of BH) : white foamy phlegm, rales and wheezing (+ shortness of breath in 2/5 with severe symp)</td>
<td>Bronchial hyperreactivity</td>
<td>5</td>
<td>5,15%</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Betlloch-Mas et al</td>
<td>2012</td>
<td>Spain</td>
<td>20</td>
<td>ECG and echo, BP, HR, lab at bsl</td>
<td>BP, HR, BG, weight: 5h after 1st dose then twice monthly/1st month, then monthly</td>
<td>No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty</td>
<td>6</td>
<td>30,0%</td>
<td>Bronchiolitis</td>
<td>Bronchiolitis</td>
<td>1</td>
<td>5,00%</td>
<td>ND</td>
</tr>
<tr>
<td>Erbay</td>
<td>2010</td>
<td>Turkey</td>
<td>16</td>
<td>Hosp for &lt; 3 months of age</td>
<td>Others over 8h (HR, BP hourly)</td>
<td>Cs cardioped</td>
<td>Lab</td>
<td>Then outpatient if no AE</td>
<td>FU: 10 days then monthly</td>
<td>No DD/AE</td>
<td>No hypoglycemia, diarrhea, wheezing, agitation, cold arms</td>
<td>0,0%</td>
<td>ND</td>
</tr>
<tr>
<td>Giachetti 2013</td>
<td>Argentina</td>
<td>30</td>
<td>Outpatient setting except in premature enfs.</td>
<td>Cardiomonitoring (ECG, HR, BP) + Lab (electrolytes, liver and BG) at initiation (+ echocardio) then monthly.</td>
<td>No severe side effects such as bradycardia or hypoglycemia</td>
<td>All AEs were minor</td>
<td>9</td>
<td>30,0%</td>
<td>Mild bronchospasm (due to bronchiolitis)</td>
<td>Bronchiolitis</td>
<td>3</td>
<td>10,00%</td>
<td>ND</td>
</tr>
<tr>
<td>Hogeling</td>
<td>2011</td>
<td>Australia</td>
<td>19</td>
<td>Bsl ECG, echocardio, lab</td>
<td>Monitoring BP HR BG at each visit every 4 weeks</td>
<td>6 months hosp for first dose at W1 and W2; AE monthly</td>
<td>Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7</td>
<td>No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchiolitis</td>
<td>Bronchiolitis</td>
<td>4</td>
</tr>
<tr>
<td>Holmes et al</td>
<td>2011</td>
<td>UK</td>
<td>31</td>
<td>Prett: cardiovasc work-up (HR, BP, RR, ECG, echocardio)</td>
<td>BP HR every 15 min for 2 hrs for 2 first doses</td>
<td>BG if clin. Symptoms</td>
<td>FU at W1 then 2 weekly</td>
<td>No major side effects</td>
<td>4</td>
<td>12,9%</td>
<td>Bronchiolitis</td>
<td>Bronchiolitis</td>
<td>1</td>
</tr>
<tr>
<td>Phillips</td>
<td>2012</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardio</td>
<td>Clin exam +/- BP, BG</td>
<td>2 SAES</td>
<td>In total 11 DD for side effect</td>
<td>51</td>
<td>27,1%</td>
<td>Bronchiolitis</td>
<td>Bronchiolitis</td>
<td>ND</td>
<td>-</td>
</tr>
</tbody>
</table>

Bronchiolitis Total | 10 | 0,27%
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernabeu-Wittel et al.[2011] Spain</td>
<td>28</td>
<td>For 2 days (hosp): BP, HR every 8h</td>
<td>BG every 12h</td>
<td>[ECG daily][Then BP, HR every 3 days][During dose escalation (12 days)][AEs recorded at 1, 3, 6, 9, 12 months.</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchitis</td>
<td>Bronchitis</td>
<td>3</td>
<td>10,71%</td>
<td>ND</td>
<td>3 TD + corrective tt (salbu + cortico)</td>
<td>Resolved without complications</td>
</tr>
<tr>
<td>Gan[2013] China</td>
<td>109</td>
<td>Initial monitoring of VS: BP HR BG once a day for 3 days; Hypertension, insomnia, agitation, aggravation of bronchitis, cold hands or feet, gastro-oesophageal pb and dry skin, all mild</td>
<td>23</td>
<td>21,1%</td>
<td>Bronchitis, aggravation</td>
<td>Bronchitis</td>
<td>2</td>
<td>1,83%</td>
<td>ND</td>
<td>2 TD</td>
<td>ND</td>
<td>None</td>
<td>Resolved</td>
</tr>
<tr>
<td>Gan[2013] China</td>
<td>109</td>
<td>Initial monitoring of VS: BP HR BG once a day for 3 days; Hypertension, insomnia, agitation, aggravation of bronchitis, cold hands or feet, gastro-oesophageal pb and dry skin, all mild</td>
<td>23</td>
<td>21,1%</td>
<td>Bronchitis, aggravation</td>
<td>Bronchitis</td>
<td>2</td>
<td>1,83%</td>
<td>ND</td>
<td>2 DD</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>Schupp[2011] Germany</td>
<td>55</td>
<td>ECG, echocardiogram[Initial monitoring of VS][2 night in-patient hosp][BG not checked][FU after 2 and 4 weeks then monthly (inc BP HR)][No hypotension, no bradycardia, no symptomatic hypoglycemia][No severe AEs</td>
<td>13</td>
<td>23,6%</td>
<td>Aggravation of bronchitis, mild</td>
<td>Bronchitis</td>
<td>1</td>
<td>1,82%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersen[2014] Denmark</td>
<td>37</td>
<td>Monitoring 1-2 D: BP, HR, BG; Echocardiography&lt;3 months[FU: W2 then 1 to 2 month-interval</td>
<td>12</td>
<td>32,4%</td>
<td>Bronchospasm (mild)</td>
<td>Bronchospasm</td>
<td>1</td>
<td>2,70%</td>
<td>ND</td>
<td>1 DD</td>
<td>Resolved after cessation of tt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claerhout[2011] Belgium</td>
<td>10</td>
<td>ECG, BP, BG</td>
<td>Between D10 and D14: ECG, BP, HR, BG</td>
<td>FU monthly: HR BP</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchostriction</td>
<td>Lower RTI</td>
<td>Bronchospasm</td>
<td>1</td>
<td>10,00%</td>
<td>ND</td>
<td>DD</td>
</tr>
<tr>
<td>Giachetti 2013 Argentina</td>
<td>30</td>
<td>Outpatient setting except in premature neonates[Cardi monitoring (ECG, HR, BP) + Lab (electrolytes, liver and BG) at initiation (+ echocardiogram then monthly).[No severe side effects such as bradycardia or hypoglycemia][All AEs were minor</td>
<td>9</td>
<td>30,0%</td>
<td>Mild bronchospasm (due to bronchiolitis)</td>
<td>Bronchospasm</td>
<td>3</td>
<td>10,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Külpi et al.[2012] Turkey</td>
<td>14</td>
<td>Basl echo and ECG</td>
<td>FU monthly (BG, ECG)</td>
<td>3</td>
<td>21,4%</td>
<td>Bronchospasm (reversible) + concomitant viral infection</td>
<td>Bronchospasm</td>
<td>1</td>
<td>7,14%</td>
<td>ND</td>
<td>Nebulizer Salbutamol trt</td>
<td>No TD/DD</td>
<td>Resolved</td>
</tr>
<tr>
<td>Külpi et al.[2012] Turkey</td>
<td>14</td>
<td>Basl echo and ECG</td>
<td>FU monthly (BG, ECG)</td>
<td>3</td>
<td>21,4%</td>
<td>Bronchospasm (reversible)</td>
<td>Bronchospasm</td>
<td>2</td>
<td>14,29%</td>
<td>ND</td>
<td>Nebulizer Salbutamol trt</td>
<td>No TD or DD</td>
<td>Resolved</td>
</tr>
<tr>
<td>Laforgia[2009] Italy</td>
<td>23</td>
<td>1-day hosp[Monitoring (BP, HR, BG) on D1][FU monthly, CBG every 10-15 d][No symptomatic decrease of HR or BP]</td>
<td>3</td>
<td>13,0%</td>
<td>Severe bronchospasm during asthmatic bronchitis</td>
<td>Bronchospasm</td>
<td>1</td>
<td>4,35%</td>
<td>2.5 months</td>
<td>1 DD</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Ozyoruk and Zengin[2014] Turkey</td>
<td>14</td>
<td>Basl, echocardiography, ECG</td>
<td>No AE during first 48th at hospital setting</td>
<td>FU D7 and every 15 days</td>
<td>1</td>
<td>7,1%</td>
<td>Bronchospasm (3 episodes)</td>
<td>Bronchospasm</td>
<td>1</td>
<td>7,14%</td>
<td>ND</td>
<td>1 TD: Treatment discontinued for 10 days at each episode</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
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<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
</tr>
<tr>
<td>--------</td>
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<td>------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Sondhi[2013]</td>
<td>India</td>
<td>31</td>
<td>Bsl lab, ECG, abdo US, echocardio if cardiac abn.</td>
<td>Hosp after 1st dose for 8h (72h for younger &lt;6 weeks):</td>
<td>- HR, BP every 30 min</td>
<td>- BG twice</td>
<td>Then HR, BP, BG weekly for the first month then monthly</td>
<td>Mean reduction by 4 mmHg for SBP, 7 mmHg for DBP, 19 bpm for HR, no associated symptoms</td>
<td>No hypoglycaemic episodes</td>
<td>3</td>
<td>9.7%</td>
<td>Bronchospasm</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Albuquerque[2014]</td>
<td>Brazil</td>
<td>69</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>23.2%</td>
<td>Precordial pain (mild)</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Graaf (de) et al[2011]</td>
<td>Netherlands</td>
<td>28</td>
<td>No catastrophic neuro events</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Constipation</td>
<td>Constipation</td>
<td>3</td>
<td>10.71%</td>
<td>ND</td>
<td>ND</td>
<td>Resolved</td>
</tr>
<tr>
<td>Hassan[2014]</td>
<td>Egypt</td>
<td>30</td>
<td>Hosp 1 or 2 first days</td>
<td>ECG, echocardio bsl Monitoring (BP, HR, BG) 2 D</td>
<td>(D1, D2): 1 to 3 times a day (before and 2h after each dose)</td>
<td>FU: every 2 weeks</td>
<td>(ECG BP HR)</td>
<td>No significant hypotension, hypoglycemia or bradycardia</td>
<td></td>
<td></td>
<td>0.0%</td>
<td>ND</td>
<td>Constipation</td>
</tr>
<tr>
<td>Metry et al.[2013]</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Constipation</td>
<td>Constipation</td>
<td>1</td>
<td>3.13%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>Xiao[2013]</td>
<td>China</td>
<td>64</td>
<td>Hosp first 3 days</td>
<td>Bsl ECG</td>
<td>Discontinuation if serious cough with dyspnea</td>
<td>FU monthly:</td>
<td>BP HR BG</td>
<td>No severe AE</td>
<td>12/13 pts with mild AEs and discontinuation</td>
<td></td>
<td></td>
<td>13</td>
<td>20.3%</td>
</tr>
<tr>
<td>Blatt et al.[2011]</td>
<td>USA</td>
<td>54</td>
<td>Bsl: ECG (if &lt; 3 months of age)</td>
<td>2 infants max dose: 4 or 5 mg/kg/d</td>
<td>6 AEs moderate to severe</td>
<td>5 AEs potentially life-threatening</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>16.7%</td>
<td>Cough (mild)</td>
<td>Cough</td>
</tr>
<tr>
<td>Blatt et al.[2011]</td>
<td>USA</td>
<td>54</td>
<td>Bsl: ECG (if &lt; 3 months of age)</td>
<td>2 infants max dose: 4 or 5 mg/kg/d</td>
<td>6 AEs moderate to severe</td>
<td>5 AEs potentially life-threatening</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>16.7%</td>
<td>Cough (mild)</td>
<td>Cough</td>
</tr>
</tbody>
</table>

<p>| Bronchospasm Total | 11 | 0.29% | | | | | | | | | | | | | | | |
| Chest pain Total | 2 | 0.05% | | | | | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th>Author</th>
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<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE (%)</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)./ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagazgoitia et al.[2011]</td>
<td>Spain/Argentina</td>
<td>71</td>
<td>Cardio exam (EKG, BP, HR) before and BP, HR: 1 to 3 times a day during the 1st 2 or 3 days. 1 to 4 weeks later: EKG, BP, HR;[B]G in 10 cases 3 times a day during the 1st 3 days. Monthly FU[No hypotension, no hypoglycemia][Mean max -7/-10 mmHg][HR: -18 bpm</td>
<td>0,0%</td>
<td>ND</td>
<td>Cyanotic breathing spells</td>
<td>Cyanosis</td>
<td>1</td>
<td>1,41%</td>
<td>ND</td>
<td>ND</td>
<td>Still present after propranolol WD</td>
</tr>
<tr>
<td>Blatt et al.[2011]</td>
<td>USA</td>
<td>54</td>
<td>Bsl. ECG (if less than 3 months of age)[2 infants max dose: 4 or 5 mg/kg/d][6 AEs moderate to severe][5 AEs potentially life-threatening]</td>
<td>9</td>
<td>16,7%</td>
<td>Acrocyanosis, mottling of lower legs, feet and hands, potentially life threatening</td>
<td>Cyanosis</td>
<td>1</td>
<td>1,85%</td>
<td>3 days of ttt (at 0.9 mg/kg/d TID)</td>
<td>ttt stopped</td>
<td>Resolved</td>
</tr>
<tr>
<td>Jian[2014]</td>
<td>China</td>
<td>97</td>
<td>Lab tests[EKG BP HR monitoring 48h after 1st dose][Hosp for 3-5 days][Monthly FU</td>
<td>0,0%</td>
<td></td>
<td>Cyanosis and cold extremities + HR/BP decreased 118˗&gt;80 bpm, 105/87 =&gt; 90/65 mmHg[SPO2 97˗99=/&gt;80-85, ECG normal</td>
<td>Cyanosis</td>
<td>1</td>
<td>1,03%</td>
<td>10 minutes after the second dose of propranolol</td>
<td>Oxygenotherapy 3 min</td>
<td>DD</td>
</tr>
<tr>
<td>Hasan[2013]</td>
<td>Bangladesh</td>
<td>36</td>
<td>BP HR for first 3h[Monthly FU][No major change in HR, no change in BP</td>
<td>0,0%</td>
<td>ND</td>
<td>Acute renal failure[following diarrhea in a patient admitted 2.5 months before for respiratory distress)</td>
<td>Death</td>
<td>1</td>
<td>2,78%</td>
<td>2.5 months after treatment initiation</td>
<td>ND</td>
<td>Death</td>
</tr>
<tr>
<td>Metry et al.[2013]</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events[No serious complication][Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td>Peripheral arteriopathy, worsening (digital infant)</td>
<td>Death</td>
<td>1</td>
<td>3,13%</td>
<td>ND</td>
<td>(1 mg/kg/d TID)</td>
<td>ND</td>
</tr>
<tr>
<td>Phillips[2012]</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardiogram exam +/- BP, BG</td>
<td>2 SAEs][In total 11 DD for side effect</td>
<td>51</td>
<td>27,1%</td>
<td>Less active and anorexic</td>
<td>Decreased activity</td>
<td>1</td>
<td>0,53%</td>
<td>ND</td>
<td>DD</td>
</tr>
<tr>
<td>Phillips[2012]</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardiogram exam +/- BP, BG</td>
<td>2 SAEs][In total 11 DD for side effect</td>
<td>51</td>
<td>27,1%</td>
<td>Less active</td>
<td>Decreased activity</td>
<td>1</td>
<td>0,53%</td>
<td>After starting propra</td>
<td>TD, positive rechallenge then DD</td>
</tr>
<tr>
<td>Rössler[2012]</td>
<td>Germany</td>
<td>30</td>
<td>Bsl echocardiogram and ECG</td>
<td>6</td>
<td>20,0%</td>
<td>Reduced activity and increased sleep period</td>
<td>Decreased activity</td>
<td>3</td>
<td>10,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Summary:**

- **Cyanosis Total:** 3 (0,08%)
- **Death Total:** 2 (0,05%)
- **Decreased activity Total:** 5 (0,13%)
<table>
<thead>
<tr>
<th>Author</th>
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<th>N patients with any AE (%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE (%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertrand [2012] Canada</td>
<td>35</td>
<td>Bsl ECG and echo, BP, HR ambulatory monitor: first 4 to 6 weeks [FU: weekly first 4-6 weeks then twice a month] [No SAE] [All AEs at low dose (&lt;2mg/kg) [No symptom, Hypoglycemia]</td>
<td>0,0% ND Decrease appetite</td>
<td>Decreased appetite</td>
<td>1 2,86% &lt;6 weeks ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betlloch-Mas et al. [2012] Spain</td>
<td>20</td>
<td>ECG and echo, BP, HR, lab at bsl [BP, HR, BG, weight: 5h after 1st dose then twice monthly] [1st month, then monthly] [No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty]</td>
<td>6 30,0% Loss of appetite</td>
<td>Decreased appetite</td>
<td>1 5,00% ND None ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Java [2011] USA</td>
<td>12</td>
<td>Bsl VS, echo cardio, ECG, BG [BG 1h after each first 2 doses] [No major complications]</td>
<td>2 16,7% Decreased appetite (due to constipation tt)</td>
<td>Decreased appetite</td>
<td>1 8,33% ND DA: Dose reduced temp. Improved</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phillips [2012] Australia</td>
<td>188</td>
<td>ECG, echocardiogram exam +/- BP, BG</td>
<td>51 27,1% Less active and anorexic</td>
<td>Decreased appetite</td>
<td>1 0,53% ND DD</td>
<td>Resolved (within 1 day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snir [2011] Israel</td>
<td>30</td>
<td>ECG echocardiogram 24h hosp with BP HR BG monitor, [+ after 1 week then every 6-8 weeks] [No abnormal finding of BP HR and BG] [DA in 3 patients]</td>
<td>11 36,7% Loss of appetite</td>
<td>Decreased appetite</td>
<td>1 3,33% ND DA to 1 mg/kg/day</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuan [2013] China</td>
<td>35</td>
<td>Hosp 3 to 5 days [Bsl lab, chest RX, ECG] [No disc for AE] [All AEs are mild] [Mild GI reactions] [No hypoglycemia or bronchospasms</td>
<td>35 100,0% Anorexia</td>
<td>Decreased appetite</td>
<td>1 2,86% ND ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauman [2014] USA</td>
<td>10</td>
<td>Bsl ECG and VS [BP, HR, BG 1 h after each dose for the first 3 doses] [Preliminary stop of study owing to severe AEs in 0 pts on propranolol vs 6/8 pts on prednisolone] [0 DD for AE on propranolol versus 5 DD for AE on prednisolone] [32 AEs on propranolol vs 44 on prednisolone Severe (CTCAE grade 3) AEs: 1 in 1 patient on propranolol vs 11 in 5 patients on prednisolone (9 decline in growth or weight, 1 adrenal crisis + viral gastro-enteritis, 1 severe dehydration warranting hosp)] [Severe growth retardation in 0 patients/propranolol vs 5 on prednisolone]</td>
<td>9 90,0% 9 (90%) [[vs 7/8=7,5% on prednisolone]</td>
<td>Dehydration (severe; warranting hosp)</td>
<td>1 10,00% ND ND but No DD</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
</tr>
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<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Hogeling[2011] Australia</td>
<td>19 Bsl ECG, echocardio, lab [Monitoring BP HR BG at each visit every 4 weeks]&lt;6 months hosp for first dose at W1 and W2; AE monthly]Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7][No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0% ND</td>
<td>Dental caries</td>
<td>Dental caries</td>
<td>1</td>
<td>5,26% ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backmiller[2010] USA</td>
<td>41 No hospitalization</td>
<td>Bsl: ECG</td>
<td>Monthly visit</td>
<td>No Aes related to cardiac ev. Bronchospasm or hypoglycemia</td>
<td>All AEs minor</td>
<td>10</td>
<td>24,4% 10/22 inquired families</td>
<td>Allergic rash (psoriatic-like)</td>
<td>Dermatitis allergic</td>
<td>1</td>
<td>2,44% ND</td>
<td>1 DD</td>
</tr>
<tr>
<td>Vassallo[2013] Italy</td>
<td>14 Cardio ev. ECG, echocardio, monthly monitoring; HR, RR, BG, sear for acrocyanosis, nightmares, drowsiness, irritability, acid backward flow[Echocardio if BP or HR abn.][FU: W1 then monthly</td>
<td>2</td>
<td>14,3%</td>
<td>Allergy; Rash (considered as an allergic cutaneous reaction to propra)</td>
<td>Dermatitis allergic</td>
<td>1</td>
<td>7,14% 3 months</td>
<td>1 DD</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price[2011] USA</td>
<td>68 Cs cardio, BP BG first 48h</td>
<td>0,0% ND</td>
<td>Nonspecific skin eruption (developed rash)</td>
<td>Dermatitis</td>
<td>2</td>
<td>2,94% ND</td>
<td>2 TD (negative rechallenge)</td>
<td>Resolved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al. Dhaybi et al.[2011] Canada</td>
<td>18 If SBP&lt;70 mmHg or HR&lt;70 bpm =&gt; propranolol was discontinued</td>
<td>13: early tt group</td>
<td>4: late-treatment group</td>
<td>Mild diarrhea</td>
<td>Diarrhoea</td>
<td>3</td>
<td>16,67% ND</td>
<td>3 None</td>
<td>Resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersen[2014] Denmark</td>
<td>37 Monitoring 1-2 D: BP, HR, BG; Echocardiography&lt;3months[FU: W2 then 1 to 2 month-interval</td>
<td>12</td>
<td>32,4%</td>
<td>Diarrhea (mild)</td>
<td>Diarrhoea</td>
<td>2</td>
<td>5,41% ND</td>
<td>1 DD</td>
<td>Resolved after cessation of tt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balma-Mena[2012] Canada</td>
<td>44 ECG, BP, HR, BG; bsl, every 2 weeks for 1st month then monthly</td>
<td>All events minor</td>
<td>14</td>
<td>31,8%</td>
<td>Vomiting + diarrhea</td>
<td>Diarrhoea</td>
<td>2</td>
<td>4,55% ND</td>
<td>2 None</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuchsmann[2011] France /Canada</td>
<td>39 Propranolol was substituted by acebutolol in 5 patients because of trouble sleeping/sleep disturbances, after 1 month of propra</td>
<td>bsl VS, HR, BP, echocardio</td>
<td>BG in 22 pts (normal)</td>
<td>[FU: 2h or 1 day][No cardiac AE, no clinical symptoms related to hypoglycemia</td>
<td>0,0% ND</td>
<td>Mild diarrhea</td>
<td>Diarrhoea</td>
<td>2</td>
<td>5,13% ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Author Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Monitoring + Safety additional results</td>
<td>N patients with any AE (%) patients with any AE (other)</td>
<td>AE Notified AE MedDRA preferred term</td>
<td>N patients with AE (%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
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<tr>
<td>Graaf (de) al. 2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses) Bas: ECG [Outpatient FU: 1, 2, 4, 8, 12 weeks] BP, HR</td>
<td>0,0% ND Diarrhea</td>
<td>Diarrhoea</td>
<td>1 3,57%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasan 2013</td>
<td>Bangladesh</td>
<td>36</td>
<td>BP HR for first 3h</td>
<td>Monthly FU</td>
<td>No major change in HR, no change in BP</td>
<td>0,0% ND Acute renal failure</td>
<td>Following diarrhea in a patient admitted 2.5 months before for respiratory distress</td>
<td>Diarrhoea</td>
<td>1 2,78%</td>
<td>Between 2 months and 2.5 months after treatment initiation</td>
<td>ND</td>
<td>Death</td>
</tr>
<tr>
<td>Hermans 2011</td>
<td>The Netherlands</td>
<td>20</td>
<td>Bas ECG, echocardiograms, BP, HR, BG during first 3 days at hosp. Evaluations every 6 weeks</td>
<td>11 55,0% Diarrhea, vomiting</td>
<td>Diarrhoea</td>
<td>1 5,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Javia 2011</td>
<td>USA</td>
<td>12</td>
<td>Basl VS, echo cardio, ECG, BG 1h after each first 2 doses</td>
<td>No major complications</td>
<td>2 16,7% Diarrhea</td>
<td>Diarrhoea</td>
<td>1 8,33%</td>
<td>ND</td>
<td>DA: Dose reduced temp.</td>
<td>Improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lao 2014</td>
<td>China</td>
<td>635</td>
<td>Hosp 3-4 days</td>
<td>“No significant/serious AE’s”</td>
<td>12/24 stopping for side effect</td>
<td>24 3,8% Diarrhea, intractable</td>
<td>Diarrhoea</td>
<td>3 0,47%</td>
<td>ND</td>
<td>ND</td>
<td>3 Resolution after it disc</td>
<td></td>
</tr>
<tr>
<td>Lv et al. 2012</td>
<td>China</td>
<td>37</td>
<td>BP, HR, ECG, BG, lab: every 2 weeks at hosp</td>
<td></td>
<td>All 37 have mildly transient decreased HR and lower BP after taking the drug with no clinical symptoms</td>
<td>No severe ADR</td>
<td>No hypoglycemia, no bronchospasms, no seizure, no adverse neurological sequelae, no apleucytosis</td>
<td>0,0% ND Diarrhea, mild</td>
<td>Diarrhoea</td>
<td>9 24,32%</td>
<td>1st week</td>
<td>None</td>
</tr>
<tr>
<td>Ma 2013</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days</td>
<td>Basl HR, SBP, DBP, SaO2, ECG, standard lab</td>
<td>Every 3 h: clin, ECG monitoring for first 3 days</td>
<td>HR BP 1h after each dose</td>
<td>FU with ASAT, ALAT, thyroid function and BG</td>
<td>Every 3 months</td>
<td>Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycemia</td>
<td>Slight decrease HR BP</td>
<td>No bronchospasms or leukocytosis</td>
<td>0,0% ND Diarrhea, mild</td>
</tr>
<tr>
<td>Meng 2012</td>
<td>China</td>
<td>22</td>
<td>Hosp 3 week</td>
<td>HRE BP I 1, 3, 6h after propranolol use</td>
<td>Lab, cardiac US, BG 3, 7, 14, 28 days after propranolol use then monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea, moderate</td>
</tr>
<tr>
<td>Phillips 2012</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardiogram, ECG exam +/- BP, BG</td>
<td>In total 11 DD for side effect</td>
<td>51 27,1% Diarrhea</td>
<td>Diarrhoea</td>
<td>6 3,19%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
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<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE (%)</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
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<tr>
<td>Snir[2011]Israel</td>
<td>30</td>
<td>ECG echocardiography 124 hours with BP HR BG monitor, 1 week then every 6-8 months [No abnormal finding of BP HR and BG] DA in 3 patients</td>
<td>11</td>
<td>36.7%</td>
<td>Diarrhea</td>
<td>Diarrhoea</td>
<td>2</td>
<td>6.67%</td>
<td>ND</td>
<td>2 DA to 1 mg/kg/day</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Szychta[2014]UK</td>
<td>60</td>
<td>Hosp 6 h (&lt;2 yrs) 48 h (&lt;2 yrs) Monitoring BP + HR 30 min after 1st dose and every 15 min during 1 h</td>
<td>0.0%</td>
<td>ND</td>
<td>Diarrhea</td>
<td>Diarrhoea</td>
<td>3</td>
<td>5.00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Xiao[2013]China</td>
<td>64</td>
<td>Hosp first 3 days Baseline ECG</td>
<td>13</td>
<td>20.3%</td>
<td>Diarrhea, mild</td>
<td>Diarrhoea</td>
<td>4</td>
<td>6.25%</td>
<td>ND</td>
<td>4 None, symptomatic tt</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Bertrand[2012]Canada</td>
<td>35</td>
<td>Baseline ECG and echo BP, HR ambulatory monitor: first 4 to 6 weeks</td>
<td>0.0%</td>
<td>ND</td>
<td>Shortness of breath on physical activity (10 yr F)</td>
<td>Dyspnea exertional</td>
<td>1</td>
<td>2.86%</td>
<td>&lt;6 weeks</td>
<td>DA (slower scale of increase)</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Albuquerque[2014]Brazil</td>
<td>69</td>
<td>Baseline ECG, BP, HR, BG: Baseline, every 2 weeks for 1st month then monthly</td>
<td>16</td>
<td>23.2%</td>
<td>Transitory dyspnea (mild)</td>
<td>Dyspnea</td>
<td>4</td>
<td>5.80%</td>
<td>ND</td>
<td>No DD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Balma-Menal[2012]Canada</td>
<td>44</td>
<td>ECG, BP, HR, BG: Baseline, every 2 weeks for 1st month then monthly</td>
<td>14</td>
<td>31.8%</td>
<td>Transient shortness of breath (+ viral illness)</td>
<td>Dyspnea</td>
<td>3</td>
<td>6.82%</td>
<td>ND</td>
<td>3 None</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Sagi[2014]Israel</td>
<td>99</td>
<td>Hosp for 3 days Baseline ECG, echocardiography before int. Monitoring BP, HR, BG Then BP, HR weekly Decrease dose by half/mild side effects = wheezing, irritability or sleep disturbance Discontinuation if SAE</td>
<td>32</td>
<td>32.3%</td>
<td>Recalcitrant dyspnea and wheezing</td>
<td>Dyspnea</td>
<td>2</td>
<td>2.02%</td>
<td>ND</td>
<td>2 DA (decrease to 1 mg/kg/d) then 2 DD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Snir[2011]Israel</td>
<td>30</td>
<td>ECG echocardiography 124 hours with BP HR BG monitor, 1 week then every 6-8 weeks</td>
<td>11</td>
<td>36.7%</td>
<td>Breathing difficulty</td>
<td>Dyspnea</td>
<td>1</td>
<td>3.33%</td>
<td>ND</td>
<td>DA to 1 mg/kg/day</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Zvulunov[2011]Australia</td>
<td>42</td>
<td>No significant side effects</td>
<td>4</td>
<td>9.5%</td>
<td>Transient dyspnea</td>
<td>Dyspnea</td>
<td>1</td>
<td>2.38%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

Diarrhoea Total: 45 (1.19%)

Dyspnea exertional Total: 1 (0.03%)

Dyspnea Total: 11 (0.29%)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE (%)</th>
<th>Patients with any AE (other)</th>
<th>AE Notified AE MedDRA preferred term</th>
<th>N patients with AE (%)</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiestl [2011] Switzerland</td>
<td>25</td>
<td>ECG, echocardiogram, HR, BP</td>
<td>[2-3-day in-patient observation at initiation] Monitoring 1h after adn of each dose: HR BP and continuous HR monitoring during sleep</td>
<td>After complete D2: ECG</td>
<td>FU after 1 week, 1 month and every 2 months (clin HR BP)</td>
<td>No relevant hemodynamic changes</td>
<td>No吐 Drop out No hypoglycemia but BG not routinely measured</td>
<td>0,0%</td>
<td>ECG changes (all mild prolongation of PQ interval)</td>
<td>ECG PQ interval prolonged</td>
<td>7</td>
</tr>
<tr>
<td>Zegbi-Trueba et al. [2012] Chile</td>
<td>57</td>
<td>ECG echocardiogram HB BP</td>
<td>Started in ambulatory way</td>
<td>At D10 24h rythm holter (none altered)</td>
<td>[FU monthly]</td>
<td>No VS FU (only symptomatic AE reported)</td>
<td>0,0%</td>
<td>Overdose (10 times the dose), serious: restless, euphoric, insomnia</td>
<td>Normal BP HR BG</td>
<td>Euphoric mood</td>
<td>1</td>
</tr>
<tr>
<td>Haider et al. [2010] USA</td>
<td>17</td>
<td>Baseline ECG</td>
<td>Monitoring BP/HR 24h after any dosage change</td>
<td>No DA or DD</td>
<td>No hypotension, no bradycardia</td>
<td>No symptomatic hypoglycemia</td>
<td>6</td>
<td>35,3%</td>
<td>Intermittent fatigue (mild)</td>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Hermans [2011] The Netherlands</td>
<td>20</td>
<td>Baseline ECG, echocardiogram, BP, HR, BG</td>
<td>During first 3 days at hosp</td>
<td>Evaluations every 6 weeks</td>
<td>11</td>
<td>55,0%</td>
<td>Temporary drowsiness/tiredness</td>
<td>Fatigue</td>
<td>6</td>
<td>30,00%</td>
<td>ND</td>
</tr>
<tr>
<td>Schupp [2011] Germany</td>
<td>55</td>
<td>ECG, echocardiogram</td>
<td>Initial monitoring of VS</td>
<td>[2 night in-patient hosp] BG not checked</td>
<td>[FU after 2 and 4 weeks then monthly (inc BP HR)]</td>
<td>No hypotension, no bradycardia, no symptomatic hypoglycemia</td>
<td>No severe AEs</td>
<td>13</td>
<td>23,6%</td>
<td>Fatigue, mild</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Hermans [2013] Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardiogram (75 first pts)</td>
<td>Tt started at home</td>
<td>Day care sitting at the target dose start</td>
<td>[FU every 6 weeks]</td>
<td>108</td>
<td>62,1%</td>
<td>Feeding difficulty</td>
<td>Feeding disorder</td>
<td>3</td>
<td>1,72%</td>
</tr>
<tr>
<td>Hogeling [2011] Australia</td>
<td>19</td>
<td>Baseline ECG, echocardiogram, lab</td>
<td>Monitoring BP HR BG at each visit every 4 weeks</td>
<td>&lt;6 months hosp for first dose at W1 and W2</td>
<td>AE monthly</td>
<td>Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7</td>
<td>No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>Gastro-enteritis (viral)</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
</tr>
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</tr>
<tr>
<td>Phillips</td>
<td>2012</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardiogram exam +/- BP, BG</td>
<td>2 SAEs</td>
<td>In total 11 DD for side effect</td>
<td>51</td>
<td>27,1%</td>
<td>Gastroenteritis</td>
<td>Gastroenteritis</td>
<td>1</td>
</tr>
<tr>
<td>Backmlnter</td>
<td>2010</td>
<td>USA</td>
<td>41</td>
<td>No hospitalization</td>
<td>Bsl: ECG</td>
<td>Monthly visit</td>
<td>No AEs related to cardiac event</td>
<td>Bronchospasm or hypoglycaemia</td>
<td>All AEs minor</td>
<td>10</td>
<td>24,4%</td>
</tr>
<tr>
<td>Dyme</td>
<td>2012</td>
<td>USA</td>
<td>15</td>
<td>Outpatients</td>
<td>6 h of observation after 1st dose</td>
<td>FU cardio at W2 and every 1-2 months</td>
<td>No hypotension, hypoglycaemia, bronchospasm, CS bradycardia</td>
<td>No complications at initiation</td>
<td>Mild decrease in HR continued throughout the 6-month FU period</td>
<td>0,0%</td>
<td>ND</td>
</tr>
<tr>
<td>Haider et al.</td>
<td>2010</td>
<td>USA</td>
<td>17</td>
<td>Bsl: ECG</td>
<td>Monitoring BP/HR 24h after any dosage change</td>
<td>No DA or DD</td>
<td>No hypotension, no bradycardia</td>
<td>No symptomatic hypoglycaemia</td>
<td>6</td>
<td>35,3%</td>
<td>Increased gastric reflux (mild)</td>
</tr>
<tr>
<td>Holmes et al.</td>
<td>2011</td>
<td>UK</td>
<td>31</td>
<td>Pret: cardiovasc work-up</td>
<td>(HR, BP, RR, ECG, ecocardiogram)</td>
<td>BP HR every 15 min for 2 hrs for 2 first doses</td>
<td>BG if clin. Symptoms</td>
<td>FU at W1 then 2 weekly</td>
<td>No major side effects</td>
<td>4</td>
<td>12,9%</td>
</tr>
<tr>
<td>Saint Jean et al.</td>
<td>2011</td>
<td>France</td>
<td>33</td>
<td>Echocardiogram</td>
<td>Monitoring BP HR monthly</td>
<td>No severe side effect</td>
<td>7</td>
<td>21,2%</td>
<td>Esophageal-reflux problem</td>
<td>Esophageal-reflux disease</td>
<td>1</td>
</tr>
<tr>
<td>Schuppl</td>
<td>2011</td>
<td>Germany</td>
<td>55</td>
<td>ECG, echocardiogram</td>
<td>Initial monitoring of VS</td>
<td>2 night in-patient hosp</td>
<td>BG not checked</td>
<td>FU after 2 and 4 weeks then monthly (inc BP HR)</td>
<td>No hypotension, no bradycardia, no symptomatic hypoglycaemia</td>
<td>No severe AEs</td>
<td>13</td>
</tr>
<tr>
<td>Lynch</td>
<td>2014</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation</td>
<td>Bsl: HR, BP, temp., BG, ECG, echocardiogram</td>
<td>Monitoring for 4H at each dose increase</td>
<td>BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose</td>
<td>FU weekly</td>
<td>BP HR</td>
<td>AEs were mild in most patients</td>
<td>Other non documented AEs were mild</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE (%)</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
<td></td>
</tr>
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<td>------------------------</td>
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<td></td>
</tr>
<tr>
<td>Bauman 2014, USA</td>
<td>10</td>
<td>Basal ECG and VS, BP, HR, BG 1 hr after each dose for the first 3 doses; premature stop of study owing to severe AEs in 0 pts on propranolol vs 6/8 pts on prednisolone; 0 DD for AE on propranolol versus 5 DD for AE on prednisolone; 32 AEs on propranolol vs 44 on prednisolone; Severe (CTCAE grade 3) AEs: 1 in 1 patient on propranolol vs 11 in 5 patients on prednisolone (9 decline in growth or weight, 1 adrenal crisis + viral gastro-enteritis, 1 severe dehydration warranting hosp); Severe growth retardation in 0 patients/propranolol vs 5 on prednisolone</td>
<td>90.0%</td>
<td>9 (90.0%); 7/8=87.5% on prednisolone</td>
<td>Gastro-intestinal SAEs</td>
<td>Gastro-intestinal reflux disease Total</td>
<td>9</td>
<td>0.24%</td>
<td>None/ Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
<td>ND/ ND but Not DD</td>
<td></td>
</tr>
<tr>
<td>Bertrand 2012, Canada</td>
<td>35</td>
<td>Basal ECG and echo; BP, HR ambulatory monitor: first 4 to 6 weeks; FU: weekly first 4-6 weeks then twice a month; No SAE; All AEs at low dose (&lt;2mg/kg); No symptom. Hypoglycemia</td>
<td>0.0%</td>
<td>ND</td>
<td>Digestive symptom</td>
<td>Gastrointestinal disorder</td>
<td>3</td>
<td>8.57%</td>
<td>&lt;6 weeks</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Gan 2013, China</td>
<td>109</td>
<td>Initial monitoring of VS: BP HR BG once a day for 3 days; Hypotension, insomnia, agitation, aggravation of bronchitis, cold hands or feet, gastro-oesophageal pain and dry skin, all mild</td>
<td>21.1%</td>
<td>23</td>
<td>Gastrointestinal problem</td>
<td>Gastrointestinal disorder</td>
<td>2</td>
<td>1.83%</td>
<td>ND</td>
<td>2 DD</td>
<td></td>
</tr>
<tr>
<td>Hermans 2013, Netherland</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts); Tt started at home; Day care sitting at the target dose start; FU every 6 weeks</td>
<td>62.1%</td>
<td>108</td>
<td>GI complaints</td>
<td>Gastrointestinal disorder</td>
<td>12</td>
<td>6.90%</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>El-Essawy 2011, Egypt</td>
<td>15</td>
<td>Hospital 1-2 weeks; Basal: BP, BG, electrolytes; FU: every 2 wks during the first 3 months then monthly; No SAE; Acceptable decrease in HR and BP during the 1st month in all patients</td>
<td>13.3%</td>
<td>2</td>
<td>&quot;Acceptable&quot; decrease in HR</td>
<td>Heart rate decreased</td>
<td>15</td>
<td>100.0%</td>
<td>Within the 1st month</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Erbay 2010, Turkey</td>
<td>16</td>
<td>Hospital for &lt; 3 months of age; Others over 8 h (HR, BP hourly); Cs cardipoed (Lab); Then outpatient if no AE; FU: 10 days then monthly; No DD/AE; No hypoglycemia, diarrhea, wheezing, agitation, cold arms</td>
<td>0.0%</td>
<td>ND</td>
<td>Decreased BP and HR (no bradycardia or hypotension)</td>
<td>Heart rate decreased</td>
<td>2</td>
<td>12.5%</td>
<td>Within the first 6th of ttt</td>
<td>None (monitoring 24h, stimulation)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
</tr>
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<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Jian(2014) China</td>
<td>97</td>
<td>Lab tests</td>
<td>ECG BP HR monitoring 48h after 1st dose</td>
<td>Hosp for 3-5 days</td>
<td>Monthly FU</td>
<td>0,0%</td>
<td>Cyanosis and cold extremities + HR/ BP decreased</td>
<td>Heart rate decreased</td>
<td>1</td>
<td>1,0%</td>
<td>10 minutes after the second dose of propranolol</td>
</tr>
<tr>
<td>Katona(2012) Hungary</td>
<td>22</td>
<td>Prett Clin exam</td>
<td>ECG BG first 48h</td>
<td>BP HR BG at all controls</td>
<td>2</td>
<td>9,1%</td>
<td>Pulse rate decreased, temporarily</td>
<td>No change in BG</td>
<td>Heart rate decreased</td>
<td>2</td>
<td>9,1%</td>
</tr>
<tr>
<td>Ma(2013) China</td>
<td>89</td>
<td>Hosp for 7 days</td>
<td>Bsl HR, SBP, DBP, SaO2, ECG, standard lab</td>
<td>Every 3 h. clin, [ECG monitoring for first 3 days]</td>
<td>HR BP 1 h after each dose</td>
<td>FU with ASAT, ALAT, thyroid function and BG</td>
<td>Every 3 months</td>
<td>Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extremities and hypoglycemia</td>
<td>Slight decrease in HR BP</td>
<td>No bronchospasms or leukocytosis</td>
<td>Heart rate decreased</td>
</tr>
<tr>
<td>Meng(2012) China</td>
<td>22</td>
<td>Hosp 1 week</td>
<td>HRE BP 1, 3, 6h after propranolol use</td>
<td>Lab, cardiac US, BG 3, 7, 14, 28 days after propranolol use then monthly</td>
<td>22</td>
<td>100,0%</td>
<td>HR slows down</td>
<td>Heart rate decreased</td>
<td>22</td>
<td>100,0%</td>
<td>Within first 3 days</td>
</tr>
<tr>
<td>Yuan(2013) China</td>
<td>35</td>
<td>Hosp 3 to 5 days</td>
<td>Bsl lab, chest RX, ECG</td>
<td>No disc for AE</td>
<td>All AEs are mild</td>
<td>Mild GI reactions</td>
<td>No hypoglycemia or bronchospasm</td>
<td>Slow heart rate</td>
<td>Heart rate decreased</td>
<td>35</td>
<td>100,0%</td>
</tr>
<tr>
<td>Metry et al.(2013) USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td>Right hemiparesis, mild (bisl imaging: mild focal vessel stenosis WO cerebral changes or infarction)</td>
<td>Hemiparesis</td>
<td>1</td>
<td>3,13%</td>
<td>2 months</td>
</tr>
<tr>
<td>El-Essawy(2011) Egypt</td>
<td>15</td>
<td>Hosp 1-2 weeks</td>
<td>Bsl. BP, BG, electrolytes</td>
<td>FU: every 2 wks during the first 3 months then monthly</td>
<td>No SAE</td>
<td>Acceptable decrease in HR and BP during the 1st month in all patients</td>
<td>2</td>
<td>13,3%</td>
<td>Hyperglycemia (mild; &gt; 140 mg/dL)</td>
<td>Hyperglycaemia</td>
<td>1</td>
</tr>
</tbody>
</table>

Heart rate decreased Total | 166 | 4,4% |
Hemiparesis Total | 1 | 0,03% |
Hyperglycaemia Total | 1 | 0,03% |
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbay[2010]</td>
<td>Turkey</td>
<td>16</td>
<td>0,0%</td>
<td>ND</td>
<td>Excessive sweating</td>
<td>1</td>
<td>6,25%</td>
<td>6 Within the first 4h of ttt</td>
<td>None</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georgountzou et al[2012]</td>
<td>Greece</td>
<td>28</td>
<td>17,9%</td>
<td>ND</td>
<td>Sweating (one episode)</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
<td>None</td>
<td>Resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sans et al[2009]</td>
<td>France</td>
<td>32</td>
<td>0,0%</td>
<td>ND</td>
<td>Profuse sweats</td>
<td>1</td>
<td>3,15%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zegbi-Trueba et al[2012]</td>
<td>Chile</td>
<td>57</td>
<td>0,0%</td>
<td>ND</td>
<td>Hyperhidrosis</td>
<td>1</td>
<td>1,75%</td>
<td>ND</td>
<td>None</td>
<td>Resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo[2014]</td>
<td>China</td>
<td>635</td>
<td>3,8%</td>
<td>Hyperkalemia</td>
<td>Hyperkalemia</td>
<td>16</td>
<td>2,52%</td>
<td>ND</td>
<td>16 Resolution after tt disc (Premature in 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauman[2014]</td>
<td>USA</td>
<td>10</td>
<td>90,0%</td>
<td>9 (90%)</td>
<td>Allergy/immunology</td>
<td>1</td>
<td>10,00%</td>
<td>ND</td>
<td>ND but No DD</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
</tr>
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<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Albuquerque [2014] Brazil</td>
<td>69</td>
<td>Bsl ECG and VS</td>
<td>BP, HR, BG 1 hr after each dose for the first 3 doses</td>
<td>Premature stop of study owing to severe AEs in 0 pts on propranolol vs 6/8 pts on prednisolone</td>
<td>90,0%</td>
<td>9/10 (90%)</td>
<td>Asymptomatic hypoglycaemia (however 0 patients reported in Table 3 in metabolic/lab AEs vs 1 on predni)</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>10,00%</td>
<td>After the first dose DA (next dose was skipped)</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Bauman [2014] USA</td>
<td>10</td>
<td>69</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>1,45%</td>
<td>ND</td>
<td>No DD (DD for inefficacy)</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El Ezzi [2014] Switzerland</td>
<td>29</td>
<td>Hospital 48H Monitoring 2 days – hospital, start tt: cardiac ultrasound + ECG, blood glucose level and renal function</td>
<td>BP HR every 30 min for 4 h</td>
<td>W1, W4 then every 3 weeks</td>
<td>HR BP</td>
<td></td>
<td>FU: W1, W4 then every 8 weeks</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>3,45%</td>
<td>after 3 months of tt</td>
<td>ND but no DD</td>
<td>Resolved</td>
</tr>
<tr>
<td>Graaf (de) et al. [2011] Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>3,57%</td>
<td>4 days after CS dose reduced to &lt; 0.1 mg/kg/day</td>
<td>ttt dose reduced and then increased to original dose (2 mg/kg/d)</td>
<td>Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassana [2014] Egypt</td>
<td>30</td>
<td>Hosp 1 or 2 first days</td>
<td>ECG echocardi bsl-monitoring (BP, HR, BG) 2 D (D1, D2): 1 to 3 times a day (before and 2h after each dose)</td>
<td>FU: every 2 weeks (ECG BP HR)</td>
<td>No significant hypotension, hypoglycaemia or bradycardia</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>3,33%</td>
<td>1 month</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laforgia [2009] Italy</td>
<td>23</td>
<td>1-day hosp</td>
<td>Monitoring (BP, HR, BG) on D1</td>
<td>FU monthly, CBG every 10-15 d</td>
<td>No symptomatic decrease of HR or BP</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>4,35%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
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<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/Not documented (ND)/Death</td>
</tr>
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</tr>
<tr>
<td>Lynch[2014]</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation</td>
<td>Bsl: HR, BP, temp., BG, ECG, echocadio Monitoring for 8H at each dose increase; BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose</td>
<td>FU weekly (BP HR)</td>
<td>AEs were mild in most patients</td>
<td>Other non documented AEs were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries</td>
<td>0,0%</td>
<td>ND</td>
<td>Symptomatic Hypoglycaemia associated with Viral infection</td>
<td>Hypoglycaemia</td>
<td>2,27%</td>
<td>ND</td>
</tr>
<tr>
<td>Lynch[2014]</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation</td>
<td>Bsl: HR, BP, temp., BG, ECG, echocadio Monitoring for 8H at each dose increase; BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose</td>
<td>FU weekly (BP HR)</td>
<td>AEs were mild in most patients</td>
<td>Other non documented AEs were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries</td>
<td>0,0%</td>
<td>ND</td>
<td>Asymptomatic nonsustained hypoglycaemia (mild)</td>
<td>Hypoglycaemia</td>
<td>6,82%</td>
<td>ND</td>
</tr>
<tr>
<td>Ma[2013]</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days</td>
<td>Bsl: HR, SBP, DBP, Sa 02, ECG, standard lab</td>
<td>Every 3 h: clin ECG monitoring for first 3 days</td>
<td>BP 1h after each dose</td>
<td>FU with ASAT, ALAT, thyroid function and BG</td>
<td>Every 3 months</td>
<td>Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycaemia</td>
<td>Slight decrease HR BP</td>
<td>No bronchospasms or leukocytosis</td>
<td>0,0%</td>
<td>Hypoglycaemia, slight</td>
</tr>
<tr>
<td>Malik[2013]</td>
<td>India</td>
<td>20</td>
<td>Short hosp 48h</td>
<td>ECG bsl, 24, 48h</td>
<td>BP, HR, BG: bsl, 1h and every 4h after each dose</td>
<td>48h</td>
<td>Higher numbers of complications in groups B and C</td>
<td>A: No hypogly or hypertension</td>
<td>B: sd cushing in 5</td>
<td>Gastroint upset in 3</td>
<td>Infection+uleration BH: 1</td>
<td>C: Cushing in 6</td>
<td>Gastroint upset: 4</td>
</tr>
<tr>
<td>Park[2014]</td>
<td>Korea</td>
<td>83</td>
<td>Bsl: Phys and lab exam, ECG, echocadio</td>
<td>3-day monitoring</td>
<td>BP HR RR and BG</td>
<td>No severe AE, no discontinuation</td>
<td>8</td>
<td>9,6%</td>
<td>Mild hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>4</td>
<td>4,82%</td>
<td>Within the first week of treatment</td>
</tr>
<tr>
<td>Phillips[2012]</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocadio</td>
<td>Clin exam +/- BP, BG</td>
<td>2 SAEs</td>
<td>In total 11 DD for side effect</td>
<td>51</td>
<td>27,1%</td>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>2</td>
<td>1,06%</td>
<td>ND</td>
</tr>
<tr>
<td>Price[2011]</td>
<td>USA</td>
<td>68</td>
<td>Cs cardio, BP BG first 48h</td>
<td>0,0%</td>
<td>ND</td>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>1,47%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
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<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
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<tr>
<td>Puttgen [2013] USA</td>
<td>50</td>
<td>USA</td>
<td>CV (SBP, DBP, HR) and BG monitoring in in-patient ttt: BSL, D1, D2, D3: before and 1h and 4h after D1-BSL=−10bpm for HR and BP = unchanged = D2 and D3&lt;8SL=−10bpm and &lt;6 mmHg for SBP and &lt;3 mmHg for DBP] Infants aged &gt;6months were more likely to exhibit bradycardia (p&lt;0.001) 7 pts had concom low BP and HR</td>
<td>50</td>
<td>100.0%</td>
<td>Asymptomatic Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>1</td>
<td>2.00%</td>
<td>Within the first 3 days</td>
<td>None</td>
<td>ND</td>
<td></td>
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<tr>
<td>Blatt et al. [2011] USA</td>
<td>54</td>
<td>USA</td>
<td>Bsl: ECG (if less than 3 months of age)]2 infants max dose: 4 or 5 mg/kg/d[6 AEs moderate to severe]5 AEs potentially life-threatening</td>
<td>9</td>
<td>16.7%</td>
<td>Hypoglycemic seizures severe, potentially life threatening (overdose: sometimes received 5 mg/kg/d, twice the intended dose)</td>
<td>Hypoglycaemic seizure</td>
<td>1</td>
<td>1.85%</td>
<td>2 weeks after ttt start</td>
<td>ttt stopped temporarily and re-challenged</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Hong [2013] Canada(+ USA)</td>
<td>45</td>
<td>Canada(+ USA)</td>
<td>Pret ECG/BP HR every 48h then weekly once target dose reached then monthly</td>
<td>3</td>
<td>6.7%</td>
<td>Hypoglycemic seizure episode] [reduced oral intake due to an URTI] BG not documented</td>
<td>Hypoglycaemic seizure</td>
<td>1</td>
<td>2.22%</td>
<td>After several months of treatment</td>
<td>Glucose therapy</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Phillips [2012] Australia</td>
<td>188</td>
<td>Australia</td>
<td>ECG, echocardioClin exam +/- BP, BG][2 SAEs][In total 11 DD for side effect</td>
<td>51</td>
<td>27.1%</td>
<td>Gross motor abnormality incl 1 “not weight-bearing” after starting of propranolol, 2 “unsteady on their feet in the morning/propra”, 1 walked at 11 months when propranolol stopped for gastroenteritis, and stopped walking when propranolol restarted, 7 delayed walking (17-20 months): 27 unusually passive more active within a</td>
<td>Hypokynesia</td>
<td>13</td>
<td>6.91%</td>
<td>ND</td>
<td>2 DD, 1 TD (positive rechallenge), 10 ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>Treated with Propranolol</td>
<td>Comments</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
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<tr>
<td>Graaf (de) al. [2011] Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses); Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Reduced intake</td>
<td>Hypophagia</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
<td>None</td>
<td>Resolved</td>
</tr>
<tr>
<td>Graaf (de) al. [2011] Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses); Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Reduced intake</td>
<td>Hypophagia</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>Hong [2013] Canada (+ USA)</td>
<td>45</td>
<td>Prett ECG/BP HR every 48h then weekly once target dose reached then monthly</td>
<td></td>
<td></td>
<td>3</td>
<td>6,7%</td>
<td>Hypoglycemic seizure episode (reduced oral intake due to an URTI) BG not documented</td>
<td>Hypophagia</td>
<td>1</td>
<td>2,22%</td>
<td>After several months of treatment</td>
<td>Glucose therapy</td>
<td>Resolved</td>
</tr>
<tr>
<td>Graaf (de) al. [2011] Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses); Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Hypoglycemia, symptomatic (less responsive &amp; nausea) (2.7 mmol/L)</td>
<td>Hyporesponsive to stimuli</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
<td>ttt stopped during hunger test</td>
<td>ND</td>
</tr>
<tr>
<td>Liu [2013] USA</td>
<td>31</td>
<td>24h hosp</td>
<td>HR BP BG bsl and 1 and 3h before/after each dose of propranolol</td>
<td>On average decrease by: HR: 5 bpm; SBP: 4 mmHg; DBP or BG; no stat sign change</td>
<td>Only HR sign attenuation over the first 3 doses</td>
<td>Conclusion: 24 h hosp for hemodynamic monitoring not necessary for safe initiation</td>
<td>No SAE</td>
<td></td>
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<tr>
<td>Al. Dhaybi et al. [2011] Canada</td>
<td>18</td>
<td>If SBP&lt;70 mmHg or HR&lt;70 bpm =&gt;propranolol was discontinued</td>
<td></td>
<td></td>
<td>7</td>
<td>38,9%</td>
<td>Significant persistent symptomatic hypotension (premature child)</td>
<td>Hypotension</td>
<td>1</td>
<td>5,56%</td>
<td>1st day (initiation of propranolol)</td>
<td>1 TD</td>
<td>Resolved</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/Not documented (ND)/Death</td>
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<tr>
<td>Bernabeu-Wittel et al. [2011] Spain</td>
<td>28</td>
<td>For 2 days ( hosp): BP, HR every 8h[BG every 12h] ECG daily; Then BP, HR every 3 days during dose escalation (12 days); AEs recorded at 1, 3, 6, 9, 12 months.</td>
<td>0,0%</td>
<td>ND</td>
<td>Hypotension, symptomatic; with lethargy 60/35</td>
<td>Hypotension</td>
<td>1</td>
<td>3,57%</td>
<td>1st month</td>
<td>DD</td>
<td>Spontaneously resolved in 30 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernabeu-Wittel et al. [2011] Spain</td>
<td>28</td>
<td>For 2 days ( hosp): BP, HR every 8h[BG every 12h] ECG daily; Then BP, HR every 3 days during dose escalation (12 days); AEs recorded at 1, 3, 6, 9, 12 months.</td>
<td>0,0%</td>
<td>ND</td>
<td>Hypotension, asymptomatic at 2mg/kg/d, (BP: 62/45; at rechallenge 1 mg/kg/d: 50/35)</td>
<td>Hypotension</td>
<td>1</td>
<td>3,57%</td>
<td>1st month</td>
<td>DA and DD (re-introduced at 1mg/kg/day, then discontinued)</td>
<td>1st episode spontaneously resolved in 15 min, 2nd episode: ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertrand [2012] Canada</td>
<td>35</td>
<td>Bsl ECG and echo; BP, HR ambulatory monitor: first 4 to 6 weeks; FU: weekly first 4-6 weeks then twice a month; [No SAE] All AEs at low dose (&lt;2mg/kg); [No symptom. Hypoglycemia]</td>
<td>0,0%</td>
<td>ND</td>
<td>Transient asymptomatic hypotension: 73/3 0, 51/42, 82/25</td>
<td>Hypotension</td>
<td>6</td>
<td>17,14%</td>
<td>&lt;6 weeks</td>
<td>ND</td>
<td>6 Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blatt et al. [2011] USA</td>
<td>54</td>
<td>Bsl: ECG (if less than 3 months of age); 2 infants max dose: 4 or 5 mg/kg/d; 6 AEs moderate to severe; 3 AEs potentially life-threatening</td>
<td>9</td>
<td>16,7%</td>
<td>Hypotension (barely arousable); severe, potentially life-threatening</td>
<td>Hypotension</td>
<td>1</td>
<td>1,85%</td>
<td>Within 2 weeks*</td>
<td>ttt stopped temporarily, then reintroduced at lower dose</td>
<td>Resolved*</td>
<td></td>
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<tr>
<td>Chik et al. [2010] Hong Kong</td>
<td>12</td>
<td>Hosp for 3 days; ECG, BP, BG; BP every hour for 3 hours; BG every day; [Visit at W1 then every 4-6 weeks]</td>
<td>3</td>
<td>25,0%</td>
<td>Hypotension, asymptomatic, transient</td>
<td>Hypotension</td>
<td>1</td>
<td>8,33%</td>
<td>ND</td>
<td>DA then TD then restarted at 2mg/kg/day</td>
<td>Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chik et al. [2010] Hong Kong</td>
<td>12</td>
<td>Hosp for 3 days; ECG, BP, BG; BP every hour for 3 hours; BG every day; [Visit at W1 then every 4-6 weeks]</td>
<td>3</td>
<td>25,0%</td>
<td>Hypotension, asymptomatic, transient</td>
<td>Hypotension</td>
<td>1</td>
<td>8,33%</td>
<td>ND</td>
<td>DA: ttt reduced to 1 mg/kg/day</td>
<td>Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>El Ezzi [2014] Switzerland</td>
<td>29</td>
<td>Hospital 48H [Monitoring 2 days – hospital, start tt: cardiac ultrasound + ECG, blood glucose level and renal function] BP HR every 30 min for 4 h; FU: W1, W4 then every 8 weeks (HR BP)&lt; 0 severe ADR [No AE after 2nd dose]</td>
<td>6</td>
<td>20,7%</td>
<td>Transient hypotension</td>
<td>Hypotension</td>
<td>4</td>
<td>13,79%</td>
<td>after the first dose</td>
<td>No DD, 2 DA: back to 1mg/kg/d</td>
<td>Resolved</td>
<td></td>
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<tr>
<td>Georgountzou et al. [2012] Greece</td>
<td>28</td>
<td>Bsl HR, BP, BG, echocardiog, ECG</td>
<td>HR, BP, BG during 1st 24h/hosp</td>
<td>HR, BP, every h for 6h post each dose; BG 1 h post-dose; [Then at W1 then monthly] [No documented bradycardia or hypoglycemia, no GI disturbance, behavioural change, sleep disturbance, or rash]</td>
<td>5</td>
<td>17,9%</td>
<td>Isolated self-limited episode of hypotension while asleep (56/23 mmHg)</td>
<td>Hypotension</td>
<td>1</td>
<td>3,57%</td>
<td>At onset of ttt</td>
<td>None</td>
<td>Resolved</td>
</tr>
<tr>
<td>Georgountzou et al. [2012] Greece</td>
<td>28</td>
<td>Bsl HR, BP, BG, echocardiog, ECG</td>
<td>HR, BP, BG during 1st 24h/hosp</td>
<td>HR, BP, every h for 6h post each dose; BG 1 h post-dose; [Then at W1 then monthly] [No documented bradycardia or hypoglycemia, no GI disturbance, behavioural change, sleep disturbance, or rash]</td>
<td>5</td>
<td>17,9%</td>
<td>Isolated self-limited episode of hypotension while asleep (63/25 mmHg)</td>
<td>Hypotension</td>
<td>1</td>
<td>3,57%</td>
<td>At onset of ttt</td>
<td>None</td>
<td>Resolved</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
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<tr>
<td>Graaf (de) et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)[Bsl: ECG][Outpatient FU: 1, 2, 4, 8, 12 weeks][BP, HR]</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Hypotension, symptomatic (cold extremities) 56/34 mmHg (normal DBP: 53 mmHg)</td>
<td>Hypotension</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
<td>Dose maintained &lt; 2 mg/kg/day</td>
</tr>
<tr>
<td>Graaf (de) et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)[Bsl: ECG][Outpatient FU: 1, 2, 4, 8, 12 weeks][BP, HR]</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Hypotension (low DBP: 33 to 54 mmHg), asymptomatic</td>
<td>Hypotension</td>
<td>15</td>
<td>53,57%</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
<td>Harper</td>
<td>2011</td>
<td>UK</td>
<td>30</td>
<td>Bsl ECG, echocardio, lab [Monitoring BP HR at 30 min intervals for a 4-h period after the first dose + at W1 at up-dosing: + BP, HR twice weekly during first 2 weeks and once weekly thereafter]</td>
<td>3</td>
<td>10,0%</td>
<td>Asymptomatic hypotension</td>
<td>Hypotension</td>
<td>3</td>
<td>10,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)[T1 started at home][Day care sitting at the target dose start][FU every 6 weeks]</td>
<td>108</td>
<td>62,1%</td>
<td></td>
<td>Hypotension [Cold extremities][Dro wsiness]</td>
<td>Hypotension</td>
<td>1</td>
<td>0,57%</td>
<td>D2</td>
<td>TD + DA</td>
</tr>
<tr>
<td>Holmes et al.</td>
<td>2011</td>
<td>UK</td>
<td>31</td>
<td>Prett: cardiovasc work-up (HR, BP, RR, ECG, echocardio)[BP HR every 15 min for 2 hrs for 2 first doses][BG if clin. Symptoms][FU at W1 then 2 weekly][No major side effects]</td>
<td>4</td>
<td>12,9%</td>
<td></td>
<td>Hypotension, asymptomatic (transient)</td>
<td>Hypotension</td>
<td>1</td>
<td>3,23%</td>
<td>At a loading dose</td>
<td>None</td>
</tr>
<tr>
<td>Liu</td>
<td>2013</td>
<td>USA</td>
<td>31</td>
<td>24h hosp[HR BP BG bsl and 1 and 3h before/after each dose of propra][On average decrease by:[HR: 5 bpm][SBP: 4 mmHg][DBP or BG: no stat sign change][Only HR sign attenuation over the first 3 doses][Conclusion: 24 h hosp for hemodynamic monitoring not necessary for safe initiation][No SAE]</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Transient asymptomatic systolic hypotension (SBP decrease below 5th percentile for age) (6 episodes)</td>
<td>Hypotension</td>
<td>5</td>
<td>16,13%</td>
<td>4/6 after the first dose, 2/6 after the 3rd dose</td>
<td>ND</td>
</tr>
<tr>
<td>Lynch</td>
<td>2014</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation[Bsl: HR, BP, temp., BG, ECG, echocardio][Monitoring for 8h at each dose increase: BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose][FU weekly (BP HR)][AEs were mild in most patients][Other non documented AEs were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries]</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Asymptomatic Hypotension (mild)</td>
<td>Hypotension</td>
<td>12</td>
<td>27,27%</td>
<td>ND</td>
<td>12 DA (&quot;precluded an increase in the dose of propranolol)</td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events[No serious complication]Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Hypotension, asymptomatic</td>
<td>Hypotension</td>
<td>1</td>
<td>3,13%</td>
<td>ND</td>
<td>ttt dose reduced</td>
</tr>
<tr>
<td>Park</td>
<td>2014</td>
<td>Korea</td>
<td>83</td>
<td>Bsl: Phys and lab exam, ECG, echocardio[3-day monitoring; BP HR RR and BG][No severe AE, no discontinuation]</td>
<td>8</td>
<td>9,6%</td>
<td>Mild hypotension, asymptomatic</td>
<td>Hypotension</td>
<td>2</td>
<td>2,41%</td>
<td>Within the first week of treatment</td>
<td>Treatment temporary discontinued then restarted at lower doses or delayed dose escalation (negative rechallenge)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Puttgen</td>
<td>2013</td>
<td>USA</td>
<td>50</td>
<td>CV (SBP, DBP, HR) and BG monitoring in in-patient tt: BSL</td>
<td>D1, D2,D3: before and 1h and 4h after[D1-BSL=--10bmp for HR and BP + unchanged =D2 and D3-BSL=--10bmp][and --6 mmHg for SBP and --3 mmHg for DBP][Infants aged &gt;6months were more likely to exhibit bradycardia (p&lt;0.001)][7 pts had concom low BP and HR</td>
<td>50</td>
<td>100,0%</td>
<td></td>
<td>Asymptomatic low DBP (50) or SBP (38)</td>
<td>Hypotension</td>
<td>50</td>
<td>100,0%</td>
<td>Within the first 3 days</td>
</tr>
<tr>
<td>Schiestl</td>
<td>2011</td>
<td>Switzerland</td>
<td>25</td>
<td>ECG, echocardo, HR, BP</td>
<td>3-day in-patient observation at initiation</td>
<td>Monitoring 1h after adm of each dose: HR BP and continuous HR monitoring during sleep</td>
<td>After complete D2: ECG</td>
<td>FU after 1 week, 1 month and every 2 months (clin HR BP)[No relevant hemodynamic changes][No tit Drop out][No hypoglycemia but BG not routinely measured</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Transient asymptomatic hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Szychta</td>
<td>2014</td>
<td>UK</td>
<td>60</td>
<td>Hosp 6h (&gt;2 yrs) 48h (&lt;2 yrs) Monitoring BP + HR 30 min after 1st dose and every 15 min during 1 h</td>
<td>Delta &gt;20%=&gt; medical review][CBG at 1 and 2h after propranolol adm (1st dose)? Each dose?): if &lt; 3ml/L=&gt; medical advice][Major effect =&gt; cessation of propra= hypotension, hypoglycaemia: 0][Minor effect = asymptomatic investigation</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td></td>
<td>Hypotension</td>
<td>1</td>
<td>1,67%</td>
<td>1st dose</td>
</tr>
<tr>
<td>Tan et al.</td>
<td>2011</td>
<td>New Zealand</td>
<td>15</td>
<td>4 hourly HR BP BG</td>
<td></td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Hypotension, asymptomatic (borderline DBP)</td>
<td>Hypotension</td>
<td>1</td>
<td>6,67%</td>
<td>On tit exposure</td>
</tr>
<tr>
<td>Vassallo</td>
<td>2013</td>
<td>Italy</td>
<td>14</td>
<td>Cardio ev, ECG, echocardo, monthly monitoring: HR, RR, BG, serach for acrocyanosis, nightmares, drowsiness, irritability, acid backward flow[Echocardo if BP or HR abn][FU: W1 then monthly</td>
<td>2</td>
<td>14,3%</td>
<td></td>
<td>Hypotension</td>
<td>Hypotension</td>
<td>1</td>
<td>7,14%</td>
<td>2 months</td>
<td>1 DD</td>
</tr>
<tr>
<td>Rössler</td>
<td>2012</td>
<td>Germany</td>
<td>30</td>
<td>Bsl echocardio and ECG</td>
<td></td>
<td>6</td>
<td>20,0%</td>
<td></td>
<td>Temporary hypotonia</td>
<td>Hypotonia</td>
<td>3</td>
<td>10,00%</td>
<td>Within the first 2 days</td>
</tr>
<tr>
<td>Bertrand</td>
<td>2012</td>
<td>Canada</td>
<td>35</td>
<td>Bsl ECG and echoBP, HR ambulatory monitor: first 4 to 6 weeks</td>
<td>FU: weekly first 4-6 weeks then twice a month[No SAE][All AEs at low dose (&lt;2mg/kg)][No symptom. Hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td></td>
<td>Increase appetite</td>
<td>Increased appetite</td>
<td>1</td>
<td>2,86%</td>
<td>&lt;6 weeks</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>Hypotension Total</th>
<th>118</th>
<th>3,13%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonia Total</td>
<td>3</td>
<td>0,08%</td>
</tr>
<tr>
<td>Increased appetite Total</td>
<td>1</td>
<td>0,03%</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Haider et al. [2010] USA</td>
<td>17</td>
<td>Bsl: ECG</td>
</tr>
<tr>
<td>Bauman [2014] USA</td>
<td>10</td>
<td>Bsl ECG and VS</td>
</tr>
<tr>
<td>Bertrand [2012] Canada</td>
<td>35</td>
<td>Bsl ECG and echo</td>
</tr>
<tr>
<td>Al. Dhaybi et al. [2011] Canada</td>
<td>18</td>
<td>If SBP&lt;70 mmHg or HR&lt;70 bpm =&gt; propranolol was discontinued</td>
</tr>
<tr>
<td>Laforgia [2009] Italy</td>
<td>23</td>
<td>1-day hosp Monitoring (BP, HR, BG) on D1</td>
</tr>
<tr>
<td>Sans et al. [2009] France</td>
<td>32</td>
<td>ECG, echocardiography</td>
</tr>
<tr>
<td>Sondhi [2013] India</td>
<td>31</td>
<td>Bsl lab, ECG, abdo US, echocardiography if cardiac abn.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Zegbi-Trueba et al.</td>
<td>2012</td>
<td>Chile</td>
</tr>
<tr>
<td>Bertrand</td>
<td>2012</td>
<td>Canada</td>
</tr>
<tr>
<td>Blatt et al.</td>
<td>2011</td>
<td>USA</td>
</tr>
<tr>
<td>Sagi</td>
<td>2014</td>
<td>Israel</td>
</tr>
<tr>
<td>Bernabeu-Wittel et al.</td>
<td>2011</td>
<td>Spain</td>
</tr>
<tr>
<td>Hong</td>
<td>2013</td>
<td>Canada + USA</td>
</tr>
<tr>
<td>Mc Gee</td>
<td>2013</td>
<td>Ireland, UK</td>
</tr>
<tr>
<td>Betiloch-Mas et al.</td>
<td>2012</td>
<td>Spain</td>
</tr>
<tr>
<td>Author Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Hong[2013]Canada</td>
<td></td>
<td>45 Prett ECG</td>
</tr>
<tr>
<td>Claerhout[2011]Belgium</td>
<td></td>
<td>10 ECG, BP, BG</td>
</tr>
<tr>
<td>Lynch[2014]Ireland</td>
<td></td>
<td>44 Hosp 48h for initiation</td>
</tr>
<tr>
<td>Zegbi-Trueba et al.[2012]Chile</td>
<td></td>
<td>57 ECG echocardiogram</td>
</tr>
<tr>
<td>Graaf (de) et al.[2011]Netherlands</td>
<td></td>
<td>28 At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
</tr>
<tr>
<td>Mahadevan[2010]Australia</td>
<td></td>
<td>10 Monitoring/hospital, 1-3D,</td>
</tr>
<tr>
<td>Graaf (de) et al.[2011]Netherlands</td>
<td></td>
<td>28 At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
</tr>
<tr>
<td>Lv et al.[2012]China</td>
<td></td>
<td>37 BP, HR, ECG, BG, lab: every 2 weeks at hosp</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Maj[2013]China</td>
<td>89</td>
<td>Hosp for 7 days</td>
</tr>
<tr>
<td>Sagi[2014]Israel</td>
<td>99</td>
<td>Hosp for 3 days</td>
</tr>
<tr>
<td>Al. Dhaybi et al[2011]Canada</td>
<td>18</td>
<td>If SBP&lt;70 mmHg or HR&lt;70 bpm =&gt;propranolol was discontinued</td>
</tr>
<tr>
<td>Bagazgoitia et al[2011]Spain/Argentina</td>
<td>71</td>
<td>Cardio exam (EKG, BP, HK) before and BP, HR: 1 to 3 times a day during the 1st 2 or 3 days. 1 to 4 weeks later: EKG, BP, HR, BG in 10 cases 3 times a day during the 1st 3 days. Monthly FU</td>
</tr>
<tr>
<td>Fuchsmann[2011]France/Canada</td>
<td>39</td>
<td>Propranolol was substituted by acebutolol in 5 patients because of trouble sleeping/sleep disturbances, after 1 month of propra</td>
</tr>
<tr>
<td>Saint Jean et al[2011]France</td>
<td>33</td>
<td>Echocardiog</td>
</tr>
<tr>
<td>Sans et al[2009]France</td>
<td>32</td>
<td>ECG, echocardiog</td>
</tr>
<tr>
<td><strong>Nightmare Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Bauman</td>
<td>2014</td>
<td>USA</td>
</tr>
<tr>
<td>Rössler</td>
<td>2012</td>
<td>Germany</td>
</tr>
<tr>
<td>Blatt et al.</td>
<td>2011</td>
<td>USA</td>
</tr>
<tr>
<td>Haider et al.</td>
<td>2010</td>
<td>USA</td>
</tr>
<tr>
<td>Phillips</td>
<td>2012</td>
<td>Australia</td>
</tr>
<tr>
<td>Zegbi-Trueba et al.</td>
<td>2012</td>
<td>Chile</td>
</tr>
</tbody>
</table>

**AE Notified**: 32 AEs on propranolol vs 44 on prednisolone | Severe (CTCAE grade 3) AEs: 1 in 1 patient on propranolol vs 11 in 5 patients on prednisolone (9 decline in growth or weight, 1 adrenal crisis + viral gastro-enteritis, 1 severe dehydration warranting hosp) | Severe growth retardation in 0 patients/propranolol vs 5 on prednisolone |
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE (%)</th>
<th>Patients with any AE (other)</th>
<th>AE Notified (Monitoring + Safety additional results)</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE (%)</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/Not documented (ND)/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graaf (de) et al. 2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)/(Bsl: ECG)/Outpatient FU: 1, 2, 4, 8, 12 weeks/ BP, HR</td>
<td>0.0% ND</td>
<td>Paleness</td>
<td>Pallor</td>
<td>1</td>
<td>3.57% ND</td>
<td>ND ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Hsu et al. 2012</td>
<td>Taiwan</td>
<td>13</td>
<td>Bsl VS/Weekly FU during uptitr. [then monthly] [No bradycardia, hypotension and hypoglycemia] [No SAE]</td>
<td>2</td>
<td>15.4%</td>
<td>Pallor, occasional episodes (no sign of poor perfusion)</td>
<td>Pallor</td>
<td>1</td>
<td>7.69% 1 month</td>
<td>DA: Dose reduced</td>
<td>Resolved</td>
</tr>
<tr>
<td>Metry et al. 2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events [No serious complication] [Some patients already reported in prior 9 publications]</td>
<td>0.0% ND</td>
<td>Peripheral arteriopathy, worsening (digital infant)</td>
<td>Peripheral arterial occlusive disease</td>
<td>1</td>
<td>3.13%</td>
<td>ND</td>
<td>ND</td>
<td>Death</td>
</tr>
<tr>
<td>Albuquerque 2014</td>
<td>Brazil</td>
<td>69</td>
<td></td>
<td>16</td>
<td>23.2%</td>
<td>Cold extremities (mild)</td>
<td>Peripheral coldness</td>
<td>2</td>
<td>2.90% ND</td>
<td>No DD</td>
<td>ND</td>
</tr>
<tr>
<td>Andersen 2014</td>
<td>Denmark</td>
<td>37</td>
<td>Monitoring 1-2 D: BP, HR, BG; Echocardiography&lt;3months/FU: W2 then 1 to 2 month-interval</td>
<td>12</td>
<td>32.4%</td>
<td>Cold hands (mild)</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>2.70%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Balma-Mena 2012</td>
<td>Canada</td>
<td>44</td>
<td>ECG, BP, HR, BG: bsl, every 2 weeks for 1st month then monthly/All events minor</td>
<td>14</td>
<td>31.8%</td>
<td>Cold hands and feet</td>
<td>Peripheral coldness</td>
<td>2</td>
<td>4.55%</td>
<td>ND</td>
<td>2 None</td>
</tr>
<tr>
<td>Betlloch-Mas et al. 2012</td>
<td>Spain</td>
<td>20</td>
<td>ECG and echo, BP, HR, lab at bsl)/BP, HR, BG, weight: 5h after 1st dose then twice monthly/1st month, then monthly/ [No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty]</td>
<td>6</td>
<td>30.0%</td>
<td>Cold feet</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>5.00%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Dyme 2012</td>
<td>USA</td>
<td>15</td>
<td>Outpatients/h of observation after 1st dose/FU cardio at W2 and every 1-2 months/No hypotension, hypoglycemia, bronchospasm, CS bradycardia/ [No complications at initiation] [Mild decrease in HR continued throughout the 6-month FU period]</td>
<td>0.0% ND</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>6.67%</td>
<td>DA: reduced to BID</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Giachetti 2013</td>
<td>Argentina</td>
<td>30</td>
<td>Outpatient setting except in premature enfts. [Cardiemonitoring (ECG, HR, BP) + Lab (electrolytes, liver and BG) at initiation (+ echocardiogram) then monthly]; [No severe side effects such as bradycardia or hypoglycemia]; [All AEs were minor]</td>
<td>9</td>
<td>30.0%</td>
<td>Cold harms and feet</td>
<td>Peripheral coldness</td>
<td>3</td>
<td>10.00%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE (%)</td>
<td>Time to AE onset</td>
<td>Measures taken:</td>
</tr>
<tr>
<td>--------------</td>
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<td>-----------------------------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>Graaf (de) et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses) Bsl: ECG</td>
<td>0,0%</td>
<td>ND</td>
<td>Hypotension, symptomatic (cold extremities) 56/34 mmHg (normal DBP: 53 mmHg)</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
</tr>
<tr>
<td>Graaf (de) et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses) Bsl: ECG</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>2</td>
<td>7,14%</td>
<td>ND</td>
</tr>
<tr>
<td>Graaf (de) et al.</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses) Bsl: ECG</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>3,57%</td>
<td>ND</td>
</tr>
<tr>
<td>Hassan</td>
<td>2014</td>
<td>Egypt</td>
<td>30</td>
<td>Hosp 1 or 2 first days ECG echocardo bsl Monitoring (BP, HR, BG) 2 D (D1, D2): 1 to 3 times a day (before and 2h after each dose) FU: every 2 weeks (ECG BP HR) No significant hypotension, hypoglycemia or bradycardia</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>3,33%</td>
<td>ND</td>
</tr>
<tr>
<td>Hermans</td>
<td>2011</td>
<td>The Netherlands</td>
<td>20</td>
<td>Bsl ECG, echocardio, BP, HR, BG during first 3 days at hosp Evaluations every 6 weeks</td>
<td>11</td>
<td>55,0%</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>6</td>
<td>30,0%</td>
<td>ND</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>108</td>
<td>62,1%</td>
<td>Hypotension</td>
<td>Cold extremities</td>
<td>Drowsiness</td>
<td>Peripheral coldness</td>
<td>1</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>108</td>
<td>62,1%</td>
<td>Cold extremities</td>
<td>Peripheral coldness</td>
<td>63</td>
<td>36,21%</td>
<td>ND</td>
</tr>
<tr>
<td>Hogeling</td>
<td>2011</td>
<td>Australia</td>
<td>19</td>
<td>Bsl ECG, echocardio, lab Monitoring BP HR BG at each visit every 4 weeks 56 months hos for first dose at W1 and W2; AE monthly Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7 No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold extremities (transient)</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>5,26%</td>
<td>ND</td>
</tr>
<tr>
<td>Jian</td>
<td>2014</td>
<td>China</td>
<td>97</td>
<td>Lab test ECG BP HR monitoring 48h after 1st dose Hosp for 3-5 days Monthly FU</td>
<td>0,0%</td>
<td>ND</td>
<td>Cyanosis and cold extremities + HR/BP decreased 118 =&gt;80 bpm, 105/87 =&gt; 90/65 mmHg SPO2 97-99 =&gt;80-85, ECG normal</td>
<td>Peripheral coldness</td>
<td>1</td>
<td>1,03%</td>
<td>10 minutes after the second dose of propranolol</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
</tr>
<tr>
<td>--------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Ma</td>
<td>2013</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days</td>
<td>Bsl HR, SBP, DBP, Sa O2, ECG, standard lab</td>
<td>Every 3 h: clin, ECG monitoring for first 3 days</td>
<td>HR BP 1h after each dose</td>
<td>FU with ASAT, ALAT, thyroid function and BG</td>
<td>Every 3 months</td>
<td>[Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycemia]</td>
<td>Sinlight decrease HR BP</td>
</tr>
<tr>
<td>McSwiney</td>
<td>2014</td>
<td>Ireland</td>
<td>20</td>
<td>Bsl: BP, BG, +/- electrolytes, and liver if clin. indic</td>
<td>ECG, echocardio (if abnormal clin exam+ history =&gt; no echo finally) =&gt; 1 pt had an ECG</td>
<td>BP: 1 and 2h after 1st dose</td>
<td>FU 2h after 1st dose</td>
<td>No SAE at FU</td>
<td>No hypoglycemia (&lt;3 mmol/l) over 2h and 1 week later</td>
<td>No hypotension (SBP or DBP &lt; 5th percentile) over 2h</td>
<td>7mmHg DBP (not clinically relevant)</td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold hands and feet, periodic (intermittent violaceous color change)</td>
<td>Peripheral coldness</td>
<td>1</td>
</tr>
<tr>
<td>Saint Jean et al.</td>
<td>2011</td>
<td>France</td>
<td>33</td>
<td>Echocardio</td>
<td>Monitoring BP HR monthly</td>
<td>No severe side effect</td>
<td>7</td>
<td>21,2%</td>
<td>Cool hands and feet</td>
<td>Peripheral coldness</td>
<td>1</td>
</tr>
<tr>
<td>Sans et al.</td>
<td>2009</td>
<td>France</td>
<td>32</td>
<td>ECG, echocardio</td>
<td>Short hosp 24h</td>
<td>Monitoring BP HR every h over 6 first h of tt</td>
<td>Evaluation after 10 days then monthly</td>
<td>Mild side effects</td>
<td>0,0%</td>
<td>ND</td>
<td>Cold hands</td>
</tr>
<tr>
<td>Schupp</td>
<td>2011</td>
<td>Germany</td>
<td>55</td>
<td>ECG, echocardio</td>
<td>Initial monitoring of VS2 night in-patient hosp</td>
<td>BG not checked</td>
<td>FU after 2 and 4 weeks then monthly</td>
<td>(inc BP HR)</td>
<td>No hypotension, no bradycardia, no symptomatic hypoglycemia</td>
<td>No severe AEs</td>
<td>13</td>
</tr>
<tr>
<td>Xiao</td>
<td>2013</td>
<td>China</td>
<td>64</td>
<td>Hosp first 3 days</td>
<td>Bsl ECG</td>
<td>Discontinuation if serious cough with dyspnea</td>
<td>FU monthly</td>
<td>BP HR BG</td>
<td>No severe AE</td>
<td>[12/13 pts with mild AEs and discontinuation</td>
<td>13</td>
</tr>
</tbody>
</table>

Peripheral coldness Total 100 2,66%
<table>
<thead>
<tr>
<th>Author/Years/Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comment (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/Not documented (ND)/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Essawy[2011]Egypt</td>
<td>15</td>
<td>Hosp 1-2 weeks</td>
<td>Bsl: BP, BG, electrolytes</td>
<td>FU: every 2 wks during the first 3 months then monthly</td>
<td>No SAE</td>
<td>Acceptable decrease in HR and BP during the 1st month in all patients</td>
<td>2</td>
<td>13,3%</td>
<td>13,3%</td>
<td>Peripheral ischemia (coldness and hypoperf of skin of trunk and lower limbs)</td>
<td>Peripheral ischemia</td>
<td>1</td>
</tr>
<tr>
<td>Herrmans[2011]The Netherlands</td>
<td>20</td>
<td>Bsl ECG, echocardio, BP, HR, BG during first 3 days at hosp. Evaluations every 6 weeks</td>
<td>11</td>
<td>55,0%</td>
<td>Poor feeding</td>
<td>2</td>
<td>10,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Bagazgottia et al.[2011]Spain/Argentina</td>
<td>71</td>
<td>Cardio exam (EKG, BP, HR) before and HP, HR: 1 to 3 times a day during the 1st 2 or 3 days. 1 to 4 weeks later: EKG, BP, HR, BG in 10 cases 3 times a day during the 1st 3 days. Monthly FU</td>
<td>0,0%</td>
<td>ND</td>
<td>Agitated sleep (nightmares or agitated dreams)</td>
<td>10</td>
<td>14,08%</td>
<td>ND</td>
<td>ND</td>
<td>1 DD (after 3 weeks of ttt)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Graaf (de) et al.[2011]Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses) Bsl: ECG</td>
<td>0,0%</td>
<td>ND</td>
<td>Restless sleep</td>
<td>Poor quality sleep</td>
<td>7</td>
<td>25,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Herrmans[2011]The Netherlands</td>
<td>20</td>
<td>Bsl ECG, echocardio, BP, HR, BG during first 3 days at hosp. Evaluations every 6 weeks</td>
<td>11</td>
<td>55,0%</td>
<td>Restless sleeping</td>
<td>Poor quality sleep</td>
<td>2</td>
<td>10,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Holmes et al.[2011]UK</td>
<td>31</td>
<td>Prett: cardiovasc work-up (HR, BP, RR, ECG, echocardio)</td>
<td>4</td>
<td>12,9%</td>
<td>Restless sleep</td>
<td>Poor quality sleep</td>
<td>1</td>
<td>3,23%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Lv et al.[2012]China</td>
<td>37</td>
<td>BP, HR, ECG, BG, lab: every 2 weeks at hosp</td>
<td>0,0%</td>
<td>ND</td>
<td>Restless sleep</td>
<td>Poor quality sleep</td>
<td>1</td>
<td>2,70%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(% patients with any AE)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(% patients with AE)</td>
<td>Time to AE onset</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>Ma</td>
<td>2013</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days[Bsl HR, SBP, DBP, Sa O2, ECG, standard lab]Every 3 h: clin, BCG monitoring for first 3 days@HR BP 1h after each dose[FU with ASAT, ALAT, thyroid function and BG]Every 3 months[Mild clin. AE in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycemia][Sligh decrease HR BP][No bronchospasms or leukocytosis]</td>
<td>0,0%</td>
<td>Restless sleep</td>
<td>Poor quality sleep</td>
<td>1</td>
<td>1,12%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Xiao</td>
<td>2013</td>
<td>China</td>
<td>64</td>
<td>Hosp first 3 days[Bsl ECG][Discontinuation if serious cough with dyspnea][FU monthly: BP HR BG][No severe AE][12/13 pts with mild AE and discontinuation]</td>
<td>13</td>
<td>20,3%</td>
<td>Restless sleep, mild</td>
<td>Poor quality sleep</td>
<td>3</td>
<td>4,69%</td>
<td>ND</td>
<td>3 None, symptomatic tt ND</td>
</tr>
<tr>
<td>Price</td>
<td>2011</td>
<td>USA</td>
<td>68</td>
<td>Cs cardio, BP BG first 48h</td>
<td>0,0%</td>
<td>ND</td>
<td>Fever</td>
<td>Pyrexia</td>
<td>2</td>
<td>2,94%</td>
<td>ND</td>
<td>2TD (negative rechallenge)</td>
</tr>
<tr>
<td>Snir</td>
<td>2011</td>
<td>Israel</td>
<td>30</td>
<td>ECG echocardio[24h hosp with BP HR BG monitor,]+ after 1 week then every 6-8 weeks[No abnormal finding of BP HR and BG][DA in 3 patients]</td>
<td>11</td>
<td>36,7%</td>
<td>[Fever (minor)]</td>
<td>Pyrexia</td>
<td>2</td>
<td>6,67%</td>
<td>ND</td>
<td>2 None</td>
</tr>
<tr>
<td>Schupp</td>
<td>2011</td>
<td>Germany</td>
<td>55</td>
<td>ECG, echocardio[Initial monitoring of VS][2 night in-patient hosp][BG not checked][FU after 2 and 4 weeks then monthly (inc BP HR)][No hypotension, no bradycardia, no symptomatic hypoglycemia][No severe AE]</td>
<td>13</td>
<td>23,6%</td>
<td>Exanthema or dry skin, mild</td>
<td>Rash or dry skin</td>
<td>3</td>
<td>5,45%</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
<td>Szychta</td>
<td>2014</td>
<td>UK</td>
<td>60</td>
<td>Hosp 6h (&gt;2 yrs) 48h (&lt;2 yrs) Monitoring BP + HR 30 min after 1st dose and every 15 min during 1 h[Delta &gt;20%=&gt; medical review][Capill. BG at 1 and 2h after propranolol adm (1st dose? Each dose?): if &lt; 3ml/L=&gt; medical advice][Major effect =&gt; cessation of propra= hypotension, hypoglycaemia][Minor effect = asymptomatic investigation]</td>
<td>0,0%</td>
<td>ND</td>
<td>Rash on the torso</td>
<td>Rash</td>
<td>1</td>
<td>1,67%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Zegbi-Trueba et al</td>
<td>2012</td>
<td>Chile</td>
<td>57</td>
<td>ECG echocardio HR BP][Started in ambulatory way][At D10 24h rythm holter (none altered)][FU monthly][No VS FU (only asymptomatic AE reported)]</td>
<td>0,0%</td>
<td>Skin rash, mild</td>
<td>Rash</td>
<td>1</td>
<td>1,75%</td>
<td>ND</td>
<td>Antihistamines added</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

**AE:** Adverse Event; **MedDRA:** Medical Dictionary for Regulatory Activities; **Dose adjustment (DA):** Dose adjustment; **Temp. disc (TD):** Temperature discussion; **Def. disc. (DD):** Definition discussion; **ND:** Not documented; **FU:** Follow-up; **BP:** Blood pressure; **HR:** Heart rate; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **Sa O2:** Oxygen saturation; **ASAT:** Aspartate aminotransferase; **ALAT:** Alanine aminotransferase; **BG:** Blood glucose; **CS:** Cardio; **BG:** Blood glucose; **BP:** Blood pressure; **HR:** Heart rate; **BG:** Blood glucose; **AE:** Adverse Event; **AE Notified:** Adverse Event Notified; **Patients with any AE (other):** Patients with any AE (other); **N patients with any AE:** Number of patients with any AE; **(% patients with any AE):** Percentage of patients with any AE; **Time to AE onset:** Time to AE onset; **Measures taken:** Measures taken.
<p>| Author | Year | Country | N. Patients | Comments (Monitoring + Safety additional results) | N patients with any AE | (%) patients with any AE | Patients with any AE (other) | AE Notified MedDRA preferred term | AE MedDRA preferred term | N patients with AE | (%) patients with AE | Time to AE onset | Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD) | Outcome: Resolved/ Not documented (ND)/ Death |
|--------|------|---------|-------------|-------------------------------------------------|------------------------|--------------------------|----------------------------|--------------------------------|--------------------------------|------------------------|----------------|----------------|----------------|-----------------------------------------------------------------|------------------------------------------------|
| Bauman | 2014 | USA     | 10          | Bsl ECG and VS][BP, HR, BG 1 hr after each dose for the first 3 doses][Premature stop of study owing to severe AEs in 0 pts on propranolol vs 6/8 pts on prednisolone][1 DD for AE on propranolol versus 5 DD for AE on prednisolone][32 AEs on propranolol vs 44 on prednisolone][Severe (CTCAE grade 3) AEs: 1 in 1 patient on propranolol vs 11 in 5 patients on prednisolone][9 decline in growth or weight, 1 adrenal crisis + viral gastro-enteritis, 1 severe dehydration warranting hosp][Severe growth retardation in 0 patients/propranolol vs 5 on prednisolone] | 9 | 90,0% | 9 (90%) | Pulmonary/respiratory disorder | Respiratory disorder | 8 | 80,00% | ND | None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD) | Resolved/ Not documented (ND)/ Death |
| Yuan   | 2013 | China   | 35          | Hosp 3 to 5 days][Bsl lab, chest RX, ECG][No disc for AE][All AEs are mild][Mild GI reactions][No hypoglycemia or bronchospasm | 35 | 100,0% | Rate of breathing slowed | Respiratory rate decreased | Respiratory rate decreased Total | 35 | 0,93% | ND | None | Resolved After 12H |
| Buckmiller | 2010 | USA     | 41          | No hospitalization][Bsl: ECG][Monthly visit][No Aes related to cardiac ev. Bronchospasm or hypoglycemia][All AEs minor | 10 | 24,4% | 10/22 inquired families | Respiratory syncytial virus exacerbation | Respiratory syncytial virus infection Total | 1 | 0,03% | ND | 1 DA | ND |
| Snir   | 2011 | Israel  | 30          | ECG echocardio][24h hosp with BP HR BG monitor,]+ after 1 week then every 6-8 weeks][No abnormal finding of BP HR and BG][DA in 3 patients] | 11 | 36,7% | RTI, severe | Respiratory tract infection | Respiratory tract infection Total | 1 | 3,33% | ND | DD | ND |
| Betlloch-Mas et al. | 2012 | Spain    | 20          | ECG and echo, BP, HR, lab at bsl][BP, HR, BG, weight: 5h after 1st dose then twice monthly/1st month, then monthly][No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty | 6 | 30,0% | Restlessness | Restlessness | Restlessness Total | 1 | 0,03% | ND | None | ND |
| Graaf (de) et al. | 2011 | Netherlands | 28          | At risk in in-patient clinic (discharged on D5 or after 10 doses)][Bsl: ECG][Outpatient FU: 1, 2, 4, 8, 12 weeks][BP, HR | 0,0% | ND | Restless during night and day | Restlessness | Restlessness Total | 1 | 3,57% | ND | ND | ND |</p>
<table>
<thead>
<tr>
<th>Author [Year]</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans [2013] Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>Tt started at home Day care sitting at the target dose start FU every 6 weeks</td>
<td>108</td>
<td>62.1%</td>
<td>More active, restless in the daytime</td>
<td>Restlessness</td>
<td>9</td>
<td>5.17%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Hermans [2013] Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>Tt started at home Day care sitting at the target dose start FU every 6 weeks</td>
<td>108</td>
<td>62.1%</td>
<td>Nocturnal restlessness</td>
<td>Restlessness</td>
<td>39</td>
<td>22.41%</td>
<td>ND</td>
<td>DA for some cases, §1 switch to atenolol 1mg/kg/d BID</td>
<td>ND</td>
<td>Improvement</td>
</tr>
<tr>
<td>Snir [2011] Israel</td>
<td>30</td>
<td>ECG echocardiography 24h hosp with BP HR BG monitor. [+ after 1 week then every 6-8 weeks] [No abnormal finding of BP HR and BG] [DA in 3 patients]</td>
<td></td>
<td>11</td>
<td>36.7%</td>
<td>Restlessness (minor)</td>
<td>Restlessness</td>
<td>3</td>
<td>10.00%</td>
<td>ND</td>
<td>3 None</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Zegbi-Trueba et al. [2012] Chile</td>
<td>57</td>
<td>ECG echocardiography HR BP [Started in ambulatory way]</td>
<td>At D10 24h rythm holter (none altered)</td>
<td>FU monthly</td>
<td>No VS FU (only symptomatic AE reported)</td>
<td>0.0%</td>
<td>Overdose (10 times the dose), serious: restless, euphoric, insomnia</td>
<td>Normal BP HR BG</td>
<td>Restlessness</td>
<td>1</td>
<td>1.75%</td>
<td>Emergency unit 24h</td>
<td>ND</td>
</tr>
<tr>
<td>Metry et al. [2013] USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Seizure, unrelated with polymicrogyria and neuronal migrational disorder and intractable epilepsy</td>
<td>Seizure</td>
<td>1</td>
<td>3.13%</td>
<td>(2.5-3 mg/kg/d TID)</td>
<td>ND</td>
<td>Resolved (during infancy)</td>
</tr>
<tr>
<td>Metry et al. [2013] USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Seizure, unrelated (with polymicrogyria and neuronal migrational disorder and intractable epilepsy)</td>
<td>Seizure</td>
<td>1</td>
<td>3.13%</td>
<td>(2 mg/kg/d TID)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Graaf (de) et al. [2011] Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>ECG</td>
<td>Outpatient FU:</td>
<td>BP, HR</td>
<td>0.0%</td>
<td>ND</td>
<td>Seizure-like incident (staring spell and tonic-clonic movements of harms and legs, unresponsive)</td>
<td>Seizure-like phenomena</td>
<td>1</td>
<td>3.57%</td>
<td>5h after 1st dose</td>
<td>ND</td>
</tr>
<tr>
<td>Andersen [2014] Denmark</td>
<td>37</td>
<td>Monitoring 1-2 D: BP, HR, BG; Echocardiography &lt;3months</td>
<td>FU: W2 then 1 to 2 month-interval</td>
<td>12</td>
<td>32.4%</td>
<td>Sleep disorders (mild)</td>
<td>Sleep disorder</td>
<td>9</td>
<td>24.32%</td>
<td>ND</td>
<td>ND</td>
<td>Resolved after cessation of tt</td>
<td></td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/Not documented (ND)/Death</td>
</tr>
<tr>
<td>-------------</td>
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<td>----------------</td>
<td>----------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Balma-Mena [2012] Canada</td>
<td>44</td>
<td>ECG, BP, HR, BG: bsl, every 2 weeks for 1st month then monthly</td>
<td>All events minor</td>
<td>14</td>
<td>31.8%</td>
<td>Disturbed sleep</td>
<td>Sleep disorder</td>
<td>3</td>
<td>6.82%</td>
<td>ND</td>
<td>3 None</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Ben-Amistai [2012] Israel</td>
<td>10</td>
<td>ECG, echocardiogram</td>
<td>BP HR BG for 3 days at hosp</td>
<td>Monthly FU</td>
<td>No abnormal findings BP HR BG</td>
<td>4</td>
<td>40.0%</td>
<td>Sleep disturbance, mild (night sleep arousing and crying.)</td>
<td>Sleep disorder</td>
<td>3</td>
<td>30.00%</td>
<td>ND</td>
<td>3 None</td>
</tr>
<tr>
<td>Bertrand [2012] Canada</td>
<td>35</td>
<td>Bsl ECG and echo</td>
<td>BP HR BG</td>
<td>Ambulatory monitor: first 4 to 6 weeks</td>
<td>FU: weekly first 4-6 weeks then twice a month</td>
<td>No AEs at low dose (&lt;2mg/kg)</td>
<td>No hypoglycemia</td>
<td>0.0%</td>
<td>ND</td>
<td>Sleep disturbance</td>
<td>Sleep disorder</td>
<td>8</td>
<td>22.86%</td>
</tr>
<tr>
<td>Betlloch-Mas et al. [2012] Spain</td>
<td>20</td>
<td>ECG and echo</td>
<td>BP HR BG, weight: 5h after 1st dose then twice monthly</td>
<td>1st month, then monthly</td>
<td>No SAE</td>
<td>All AEs at low dose (&lt;2mg/kg)</td>
<td>No hypoglycemia</td>
<td>6</td>
<td>30.0%</td>
<td>Disordered sleep</td>
<td>Sleep disorder</td>
<td>1</td>
<td>5.00%</td>
</tr>
<tr>
<td>Dyme [2012] USA</td>
<td>15</td>
<td>Outpatients</td>
<td>6 h of observation after 1st dose</td>
<td>FU cardio at W2 and every 1-2 months</td>
<td>No hypotension, hypoglycemia, bronchospasm, CS bradycardia</td>
<td>No complications at initiation</td>
<td>Mild decrease in HR continued throughout the 6-month FU period</td>
<td>0.0%</td>
<td>ND</td>
<td>Increased sleep</td>
<td>Sleep disorder</td>
<td>2</td>
<td>13.33%</td>
</tr>
<tr>
<td>Fuchsmann [2011] France /Canada</td>
<td>39</td>
<td>Propranolol was substituted by acebutolol in 5 patients</td>
<td>because of trouble sleeping/sleep disturbances, after 1 month of propra</td>
<td>bsl VS, HR, BP, echocardio</td>
<td>BG in 22 pts (normal)</td>
<td>FU: 2h or 1 day</td>
<td>No cardiac AE, no clinical symptoms related to hypoglycemia</td>
<td>0.0%</td>
<td>ND</td>
<td>Sleep disturbances (nightmares and frequent awakenings)</td>
<td>Sleep disorder</td>
<td>5</td>
<td>12.82%</td>
</tr>
<tr>
<td>Hogeling [2011] Australia</td>
<td>19</td>
<td>Bsl ECG, echocardio, lab</td>
<td>Monitoring BP HR BG at each visit every 4 weeks</td>
<td>&lt;6 months hosp for first dose at W1 and W2; AE monthly</td>
<td>Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7</td>
<td>No significant hypotension, bradycardia or hypoglycemia</td>
<td>0.0%</td>
<td>ND</td>
<td>Sleep disturbances</td>
<td>Sleep disorder</td>
<td>2</td>
<td>10.53%</td>
<td>ND</td>
</tr>
<tr>
<td>Hong [2013] Canada (+ USA)</td>
<td>45</td>
<td>Pret ECG</td>
<td>BP HR every 48h then weekly</td>
<td>once target dose reached then monthly</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>6.7%</td>
<td>Listlessness</td>
<td>Sleep disorder</td>
<td>1</td>
<td>2.22%</td>
</tr>
<tr>
<td>McGee [2013] Ireland, UK</td>
<td>24</td>
<td>Bsl: cardiovasc and resp exam, lab including BG, thyroid fct test, ECG echocard, abdo US</td>
<td>All infants but one tolerated the initial dose &amp; had their dose escalated</td>
<td>No hypoglycemia, gastro-intestinal upset and bronchospasm</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>16.7%</td>
<td>Disturbed sleep/poor sleep/disrupted sleep</td>
<td>Sleep disorder</td>
<td>1</td>
<td>4.17%</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Meng</td>
<td>2012</td>
<td>China</td>
<td>22</td>
<td>Hosp 1 week</td>
<td>HRE BP 1, 3, 6h after propranolol use</td>
<td>int. Lab, cardiac US, BG 3, 7, 14, 28 days after propranolol use then monthly</td>
<td>22</td>
<td>100.0%</td>
<td>Sleep change</td>
<td>Sleep disorder</td>
<td>5</td>
<td>22.73%</td>
<td>Within first 2 weeks</td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Night terrors</td>
<td>Sleep disorder</td>
<td>1</td>
<td>3.13%</td>
<td>ND</td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Sleep disturbances, mild</td>
<td>Sleep disorder</td>
<td>1</td>
<td>3.13%</td>
<td>ND</td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0.0%</td>
<td>ND</td>
<td>Sleep disturbances, severe</td>
<td>Sleep disorder</td>
<td>1</td>
<td>3.13%</td>
<td>One month</td>
</tr>
<tr>
<td>Phillips</td>
<td>2012</td>
<td>Australia</td>
<td>188</td>
<td>ECG, echocardiography (Clin exam +/- BP, BG)</td>
<td>In total 11 DD for side effect</td>
<td>51</td>
<td>27.1%</td>
<td>Sleep disturbances (incl. waking screaming at night only when they were taking propra)</td>
<td>Sleep disorder</td>
<td>26</td>
<td>13.83%</td>
<td>ND</td>
<td>Several DA: evening dose deleted</td>
</tr>
<tr>
<td>Rössler</td>
<td>2012</td>
<td>Germany</td>
<td>30</td>
<td>Bsl echocardiogram and ECG</td>
<td></td>
<td>6</td>
<td>20.0%</td>
<td>Reduced activity and increased sleep period</td>
<td>Sleep disorder</td>
<td>3</td>
<td>10.00%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Sagi</td>
<td>2014</td>
<td>Israel</td>
<td>99</td>
<td>Hosp for 3 days</td>
<td>ECG, echocardiography before int.</td>
<td>Monitoring BP, HR, BG</td>
<td>Then BP, HR weekly</td>
<td>Decrease dose by half/mild side effects= wheezing, irritability or sleep disturbance</td>
<td>Discontinuation if SAE</td>
<td>32% of patients had mild side effects</td>
<td>32</td>
<td>32.3%</td>
<td>Sleep disturbance and/or irritability</td>
</tr>
<tr>
<td>Schiestl</td>
<td>2011</td>
<td>Switzerland</td>
<td>25</td>
<td>ECG, echocardiogram, HR, BP</td>
<td>3-day in-patient observation at initiation</td>
<td>Monitoring 1h after adm of each dose: HR BP and continuous HR monitoring during sleep</td>
<td>After complete D2: ECG/FU after 1 week, 3 month and every 2 months (clin HR BP)</td>
<td>No relevant hemodynamic changes</td>
<td>No Drop out</td>
<td>No hypoglycemia but BG not routinely measured</td>
<td>0.0%</td>
<td>Sleep disturbance, reported once, mild, transient</td>
<td>Sleep disorder</td>
</tr>
<tr>
<td>Snir</td>
<td>2011</td>
<td>Israel</td>
<td>30</td>
<td>ECG echocardiogram</td>
<td>24h hosp with BP HR BG monitor,</td>
<td>+ after 1 week then every 6-8 weeks</td>
<td>No abnormal finding of BP HR and BG</td>
<td>DA in 3 patients</td>
<td>11</td>
<td>36.7%</td>
<td>Transient episode of sleep problems (minor)</td>
<td>Sleep disorder</td>
<td>3</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE (%)</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/Not documented (ND)/Death</td>
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<tr>
<td>Szychta</td>
<td>2014</td>
<td>UK</td>
<td>60</td>
<td>Hosp 6h (&gt;2 yrs) 48h (&lt;2 yrs) Monitoring BP + HR 30 min after 1st dose and every 15 min during 1 h; Delta &gt;20% =&gt; medical review; CBG at 1 and 2 h after propranolol adm (1st dose? Each dose?): if &lt; 3ml/L =&gt; medical advice; Major effect =&gt; cessation of propra= hypotension, hypoglycaemia; 0</td>
<td>Minor effect = asymptomatic investigation</td>
<td>0,0%</td>
<td>ND</td>
<td>Sleep disturbance</td>
<td>Sleep disorder</td>
<td>2</td>
<td>3,33%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Zvulunov</td>
<td>2011</td>
<td>Australia/Various</td>
<td>42</td>
<td>No significant side effects</td>
<td>4</td>
<td>9,5%</td>
<td>ND</td>
<td>Sleep disturbance (transient nightmare and sleepwalking)</td>
<td>Sleep disorder</td>
<td>2</td>
<td>4,76%</td>
<td>ND</td>
<td>2 None</td>
</tr>
<tr>
<td>Blatt et al.</td>
<td>2011</td>
<td>USA</td>
<td>54</td>
<td>Bsl: ECG (if less than 3 months of age) 2 infants max dose: 4 or 5 mg/kg/d! AEs moderate to severe; 5 AEs potentially life-threatening</td>
<td>9</td>
<td>16,7%</td>
<td>ND</td>
<td>Somnolence (with 2 patients being barely arousable= severe, potentially life-threatening [1 patient with capillary malformation = not IH]; 1 patient=sleeper°)</td>
<td>Somnolence</td>
<td>3</td>
<td>5,56%</td>
<td>2 days/ within 2 weeks**</td>
<td>Stopped, not rechallenged/ ttt stopped temporarily, then reintroduced at lower dose° /DA (dose reduced) and rechallenged°</td>
</tr>
<tr>
<td>Buckmiller</td>
<td>2010</td>
<td>USA</td>
<td>41</td>
<td>No hospitalization</td>
<td>Bsl: ECG</td>
<td>Monthly vital</td>
<td>No Aes related to cardiac ev. Bronchospasm or hypoglycaemia</td>
<td>All AEs minor</td>
<td>10</td>
<td>24,4%</td>
<td>10/22 inquired families</td>
<td>Somnolence</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Chai</td>
<td>2011</td>
<td>China</td>
<td>27</td>
<td>Pre-trt HR, BP, ECG, abdo US, lab and BG</td>
<td>Post-dose vital signs and BG</td>
<td>FU: W1 and W2 then monthly</td>
<td>0,0%</td>
<td>ND</td>
<td>Drowsiness WITH no fluctuations on vital signs</td>
<td>Somnolence</td>
<td>7</td>
<td>25,93%</td>
<td>ND</td>
</tr>
<tr>
<td>Giachetti</td>
<td>2013</td>
<td>Argentina</td>
<td>30</td>
<td>Outpatient setting except in premature enfs.</td>
<td>Cardiomonitoring (ECG, HR, BP) + Lab (electrolytes, liver and BG) at initation (+ echocardo) then monthly.</td>
<td>No severe side effects such as bradycardia or hypoglycaemia</td>
<td>All AEs were minor</td>
<td>9</td>
<td>30,0%</td>
<td>Somnolence</td>
<td>Somnolence</td>
<td>2</td>
<td>6,67%</td>
</tr>
<tr>
<td>Hermans</td>
<td>2011</td>
<td>The Netherlands</td>
<td>20</td>
<td>Bsl ECG, echocardo,</td>
<td>BP, HR, BG during first 3 days at hosp.</td>
<td>Evaluations every 6 weeks</td>
<td>11</td>
<td>55,0%</td>
<td>Temporary drowsiness/tiredness</td>
<td>Somnolence</td>
<td>6</td>
<td>30,00%</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified (Monitoring + Safety additional results)</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
</tr>
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<td>--------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherla nds</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts) T.t started at home</td>
<td>Day care sitting at the target dose start</td>
<td>FU every 6 weeks</td>
<td>108</td>
<td>62.1%</td>
<td>Hypotension</td>
<td>Cold extremities</td>
<td>Drowsiness</td>
<td>Somnolence</td>
<td>1</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherla nds</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts) T.t started at home</td>
<td>Day care sitting at the target dose start</td>
<td>FU every 6 weeks</td>
<td>108</td>
<td>62.1%</td>
<td>Less active, sleepy, drowsy</td>
<td>Somnolence</td>
<td>27</td>
<td>15.52%</td>
<td>ND</td>
</tr>
<tr>
<td>Malik</td>
<td>2013</td>
<td>India</td>
<td>20</td>
<td>Short hosp 48h</td>
<td>ECG bsl, 24, 48h</td>
<td>BP, HR, BG: bsl, 1h and every 4h after each dose</td>
<td>48h</td>
<td>Higher numbers of complications in groups B and C</td>
<td>A: No hypogly or hypotension</td>
<td>B: sd cushing in 5</td>
<td>Gastrint upset in 3</td>
<td>Infection+ulceration IH: 1</td>
<td>C:Cushing in 6</td>
</tr>
<tr>
<td>Park</td>
<td>2014</td>
<td>Korea</td>
<td>83</td>
<td>Bsl: Phys and lab exam, ECG, echocardio</td>
<td>3-day monitoring: BP HR RR and BG</td>
<td>No severe AE, no discontinuation</td>
<td>0,0%</td>
<td>Mild somnolence</td>
<td>Somnolence</td>
<td>1</td>
<td>1,20%</td>
<td>Within the first week of treatment</td>
<td>1 Treatment temporary discontinued then restarted at lower doses or delayed dose escalation (negative rechallenge)</td>
</tr>
<tr>
<td>Schiestl</td>
<td>2011</td>
<td>Switzerland</td>
<td>25</td>
<td>ECG, echocardio, HR, BP</td>
<td>2-3-day in-patient observation at initiation</td>
<td>Monitoring 1h after adm of each dose: HR BP and continuous HR monitoring during sleep</td>
<td>After complete D2: ECG/FU after 1 week, 1 month and every 2 months (clin HR BP)</td>
<td>No relevant hemodynamic changes</td>
<td>No ti Drop out</td>
<td>No hypoglycemia but BG not routinely measured</td>
<td>0,0%</td>
<td>Sleepiness, reported once, mild, transient</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Zegbi-Trueba et al.</td>
<td>2012</td>
<td>Chile</td>
<td>57</td>
<td>ECG echocardio HR BP</td>
<td>Started in ambulatory way</td>
<td>At D10 24h rythm holter (none altered)</td>
<td>FU monthly</td>
<td>No VS FU (only symptomatic AE reported)</td>
<td>0,0%</td>
<td>Sleepiness /Somnolence, mild (normal BG 104 mg/dL and BP 120/60, HR 140 bpm)</td>
<td>Somnolence</td>
<td>1</td>
<td>1,75%</td>
</tr>
<tr>
<td>Zvulunov</td>
<td>2011</td>
<td>Australia</td>
<td>42</td>
<td>EC</td>
<td>42</td>
<td>No significant side effects</td>
<td>4</td>
<td>9.5%</td>
<td>Somnolence</td>
<td>Somnolence</td>
<td>1</td>
<td>2.38%</td>
<td>ND</td>
</tr>
<tr>
<td>Hogeling</td>
<td>2011</td>
<td>Australia</td>
<td>19</td>
<td>Bsl ECG, echocardio, lab</td>
<td>Monitoring BP HR BG at each visit every 4 weeks</td>
<td>&lt;6 months hosp for first dose at W1 and W2; AE monthly</td>
<td>Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7</td>
<td>No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>Streptococcal infection</td>
<td>Streptococcal infection</td>
<td>1</td>
</tr>
</tbody>
</table>

Somnolence Total: 63, 1.67%
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagazgoitia et al.[2011]Spain/Argentina</td>
<td>71</td>
<td></td>
<td></td>
<td>Cardio exam (EKG, BP, HR) before and BP, HR: 1 to 3 times a day during the 1st 2 or 3 days. Monthly FU: No hypotension, no hypoglycemia; Mean max -7/-10 mmHg; HR: -18 bpm</td>
<td>0,0%</td>
<td>ND</td>
<td>Stridor</td>
<td>Stridor</td>
<td>1</td>
<td>1,41%</td>
<td>ND</td>
<td>IDD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Price[2011]USA</td>
<td>68</td>
<td></td>
<td></td>
<td>Cs cardio, BP BG first 48h</td>
<td>0,0%</td>
<td>ND</td>
<td>Tachycardia</td>
<td>Tachycardia</td>
<td>1</td>
<td>1,47%</td>
<td>ND</td>
<td>1TD (negative rechallenge)</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Hassan[2014]Egypt</td>
<td>30</td>
<td></td>
<td></td>
<td>Hosp 1 or 2 first days; ECG echocardio bsl Monitoring (BP, HR, BG) 2 D (D1, D2): 1 to 3 times a day before and 2h after each dose; FU: every 2 weeks (ECG BP HR); No significant hypotension, hypoglycemia or bradycardia</td>
<td>0,0%</td>
<td>ND</td>
<td>Tachycardia + Tachypnea</td>
<td>Tachypnea</td>
<td>2</td>
<td>6,67%</td>
<td>Both 2 weeks after tt</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Hsu et al.[2012]Taiwan</td>
<td>13</td>
<td></td>
<td></td>
<td>Bsl VS; Weekly FU during uptitr. then monthly; No bradycardia, hypotension and hypoglycemia</td>
<td>2</td>
<td>15,4%</td>
<td>Tachyplea, occasional (no subsequent resp distress or desaturation)</td>
<td>Tachypnea</td>
<td>1</td>
<td>7,69%</td>
<td>3 months</td>
<td>DA: Dose reduced</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Meng[2012]China</td>
<td>22</td>
<td></td>
<td></td>
<td>Hosp 1 week; HRE BP 1, 3, 6h after propranolol use; Lab, cardiac US, BG 3, 7, 14, 28 days after propranol use then monthly</td>
<td>22</td>
<td>100,0%</td>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia</td>
<td>1</td>
<td>4,55%</td>
<td>At 2 weeks</td>
<td>ND</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Giachetti 2013Argentina</td>
<td>30</td>
<td></td>
<td></td>
<td>Outpatient setting except in preterm enfs.; Cardi monitoring (ECG, HR, BP) + Lab (electrolytes, liver and BG) at initiation (+ echocardio) then monthly; No severe side effects such as bradycardia or hypoglycemia; All AEs were minor</td>
<td>9</td>
<td>30,0%</td>
<td>Mild increase in transaminases</td>
<td>Transaminases increased</td>
<td>1</td>
<td>3,33%</td>
<td>ND</td>
<td>ND</td>
<td>Resolved (after treatment completion)</td>
<td></td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE (%)</td>
<td>Patients with any AE (other)</td>
<td>AE Notified AE MedDRA preferred term</td>
<td>N patients with AE (%)</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
<td></td>
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<tr>
<td>Ma</td>
<td>2013</td>
<td>China</td>
<td>89</td>
<td>Hosp for 7 days</td>
<td>Bsl HR, SBP, DBP, SaO2, ECG, standard lab</td>
<td>Every 3 h: clin, ECG monitoring for first 3 days</td>
<td>HR BP 1h after each dose</td>
<td>FU with ASAT, ALAT, thyroid function and BG</td>
<td>Every 3 months</td>
<td>Mild clin. AEs in 12 patients: diarrhea, restless sleep, nausea, cold extr and hypoglycemia</td>
<td>Light decrease HR BP</td>
<td>0,0%</td>
<td>Transaminases increased: ASAT ALAT slightly elevated</td>
<td>5</td>
</tr>
<tr>
<td>Haider et al.</td>
<td>2010</td>
<td>USA</td>
<td>17</td>
<td>Baseline ECG</td>
<td>Monitoring BP/HR 24h after any dosage change</td>
<td>No DA or DD</td>
<td>No hypotension, no bradycardia</td>
<td>No symptomatic hypoglycemia</td>
<td>6</td>
<td>35,3%</td>
<td>shakiness (mild)</td>
<td>Tremor</td>
<td>1</td>
<td>5,88%</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>Tt started at home</td>
<td>Day care sitting at the target dose start</td>
<td>FU every 6 weeks</td>
<td>108</td>
<td>62,1%</td>
<td>Wheezing during URTI</td>
<td>URTI</td>
<td>16</td>
<td>9,20%</td>
<td>ND</td>
</tr>
<tr>
<td>Hegeling</td>
<td>2011</td>
<td>Australia</td>
<td>19</td>
<td>Baseline ECG, echocardio, lab</td>
<td>Monitoring BP HR BG at each visit every 4 weeks</td>
<td>&lt;6 months hosp for first dose at W1 and W2; AE monthly</td>
<td>Monitoring BP HR BG hourly intervals for a 4-h period after the first dose at D1 and D7</td>
<td>No significant hypotension, bradycardia or hypoglycemia</td>
<td>0,0%</td>
<td>ND</td>
<td>URTI (viral; no wheezing)</td>
<td>URTI</td>
<td>1</td>
<td>5,26%</td>
</tr>
<tr>
<td>Hong</td>
<td>2013</td>
<td>Canada/(+ USA)</td>
<td>45</td>
<td>Prett ECG</td>
<td>BP HR every 48h then weekly once target dose reached then monthly</td>
<td>3</td>
<td>6,7%</td>
<td>Hypoglycemic seizure episode</td>
<td>Reduced oral intake due to an URTI</td>
<td>BG not documented</td>
<td>URTI</td>
<td>1</td>
<td>2,22%</td>
<td>After several months of treatment</td>
</tr>
<tr>
<td>Price</td>
<td>2011</td>
<td>USA</td>
<td>68</td>
<td>Cs cardio, BP BG first 48h</td>
<td>0,0%</td>
<td>ND</td>
<td>Viral URTI</td>
<td>URTI</td>
<td>1</td>
<td>1,47%</td>
<td>ND</td>
<td>1TD (negative rechallenge)</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>Metry et al.</td>
<td>2013</td>
<td>USA</td>
<td>32</td>
<td>No catastrophic neuro events</td>
<td>No serious complication</td>
<td>Some patients already reported in prior 9 publications</td>
<td>0,0%</td>
<td>ND</td>
<td>Progressive vessel stenosis from mild to severe</td>
<td>Vascular stenosis</td>
<td>1</td>
<td>3,13%</td>
<td>8 months</td>
<td>2 mg/kg/d TID</td>
</tr>
<tr>
<td>Balma-Mena</td>
<td>2012</td>
<td>Canada</td>
<td>44</td>
<td>ECG, BP, HR, BG: bsl, every 2 weeks for 1st month then monthly</td>
<td>All events minor</td>
<td>14</td>
<td>31,8%</td>
<td>Transient shortness of breath (+ viral illness)</td>
<td>Viral infection</td>
<td>3</td>
<td>6,82%</td>
<td>ND</td>
<td>3 None</td>
<td>ND</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/ Not documented (ND)/ Death</td>
<td></td>
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</tr>
<tr>
<td>Graaf (de) et al. [2011]</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Viral infection</td>
<td>1</td>
<td>3,57%</td>
<td>After initiation of ttt</td>
<td>DD</td>
</tr>
<tr>
<td>Graaf (de) et al. [2011]</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td>Outpatient FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Viral infection</td>
<td>2</td>
<td>7,14%</td>
<td>2 After initiation of ttt</td>
<td>2 TD</td>
</tr>
<tr>
<td>Küpeli et al. [2012]</td>
<td>Turkey</td>
<td>14</td>
<td>Bsl echo and ECG</td>
<td>FU monthly (BG, ECG)</td>
<td></td>
<td></td>
<td>3</td>
<td>21,4%</td>
<td>Bronchospasm (reversible) + concomitant viral infection</td>
<td>Viral infection</td>
<td>1</td>
<td>7,14%</td>
<td>ND</td>
<td>Nebulizer Salbutamol ttt</td>
</tr>
<tr>
<td>Lynch [2014]</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation</td>
<td>Bsl: HR, BP, temp., BG, ECG, echocardio</td>
<td>Monitoring for SH at each dose increase: BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose</td>
<td>FU weekly (BP HR)</td>
<td>AE were mild in most patients</td>
<td>Other non documented AEs were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries</td>
<td>Symptomatic Hypoglycaemia associated with Viral infection</td>
<td>Viral infection</td>
<td>1</td>
<td>2,27%</td>
<td>ND</td>
<td>1 DD (after 48 weeks)</td>
</tr>
<tr>
<td>Xiao [2013]</td>
<td>China</td>
<td>64</td>
<td>Hosp first 3 days</td>
<td>Bsl ECG</td>
<td>Discontinuation if serious cough with dyspnea</td>
<td>FU monthly: BP HR BG</td>
<td>No severe AE</td>
<td>[12/13 pts with mild AEs and discontinuation]</td>
<td>Asthma aggravation “temporary aggravation of pre-existing bronchial asthma” “bronchial hyperreactivity during viral infection”</td>
<td>Viral infection</td>
<td>1</td>
<td>1,56%</td>
<td>ND</td>
<td>1 DD</td>
</tr>
</tbody>
</table>

**Total**

| Viral infection Total | 9 | 0,24% |

<p>| Balma-Mena [2012] | Canada | 44 | ECG, BP, HR, BG: bsl, every 2 weeks for 1st month then monthly | All events minor | | | 14 | 31,8% | Vomiting + diarrhea | Vomiting | 2 | 4,55% | ND | 2 None | ND |
| Graaf (de) et al. [2011] | Netherlands | 28 | At risk in in-patient clinic (discharged on D5 or after 10 doses) | Bsl: ECG | Outpatient FU: 1, 2, 4, 8, 12 weeks | BP, HR | 0,0% | ND | Vomiting | Vomiting | 1 | 3,57% | ND | None | ND |</p>
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE</th>
<th>(%) patients with any AE</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE</th>
<th>(%) patients with AE</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</th>
<th>Outcome: Resolved/Not documented (ND)/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans[2011]The Netherlands</td>
<td>20</td>
<td>Bsl ECG, echocardo, [BP, HR, BG during first 3 days at hosp.] Evaluations every 6 weeks</td>
<td></td>
<td>11</td>
<td>55,0%</td>
<td>Diarrhoea, vomiting</td>
<td>Vomiting</td>
<td>1</td>
<td>5,00%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Lynch[2014]Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation[Bsl: HR, BP, temp., BG, ECG, echocardo] Monitoring for 8H at each dose increase: BP, HR: every 30 min for 4h, then hourly: BG 1h and 2h after each dose [FU weekly (BP HR) AE's were mild in most patients] Other non documented AE's were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries</td>
<td>0,0%</td>
<td>ND</td>
<td>Vomiting associated with gastro-esophageal reflux disease</td>
<td>Vomiting</td>
<td>1</td>
<td>2,27%</td>
<td>With each dose of propranolol</td>
<td>1 TD (after 9 weeks)</td>
<td>Resolved (negative rechallenge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phillips[2012]Australia</td>
<td>188</td>
<td>ECG, echocardo, Clin exam +/- BP, BG</td>
<td></td>
<td>51</td>
<td>27,1%</td>
<td>Vomiting</td>
<td>Vomiting</td>
<td>1</td>
<td>0,53%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Sag[2014]Israel</td>
<td>99</td>
<td>Hosp for 3 days]ECG, echocardo before init. Monitoring BP, HR, BG</td>
<td>Then BP, HR weekly Decrease dose by half/mild side effects = wheezing, irritability or sleep disturbance</td>
<td>Discontinuation if SAE</td>
<td>32</td>
<td>32,3%</td>
<td>Nausea+vomiting</td>
<td>Vomiting</td>
<td>1</td>
<td>1,01%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Smir[2011]Israel</td>
<td>30</td>
<td>ECG echocardo]24h hosp with BP HR BG monitor, + after 1 week then every 6-8 weeks [No abnormal finding of BP HR and BG] DA in 3 patients]</td>
<td>11</td>
<td>36,7%</td>
<td>Vomiting</td>
<td>Vomiting</td>
<td>2</td>
<td>6,67%</td>
<td>ND</td>
<td>2 DA to 1 mg/kg/day</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuquerque[2014]Brazil</td>
<td>69</td>
<td></td>
<td></td>
<td>16</td>
<td>23,2%</td>
<td>Slow weight gain (mild)</td>
<td>Weight gain poor</td>
<td>2</td>
<td>2,90%</td>
<td>ND</td>
<td>No DD</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Bertrand[2012]Canada</td>
<td>35</td>
<td>Bsl ECG and echo]BP, HR ambulatory monitor: first 4 to 6 weeks]FU: weekly first 4-6 weeks then twice a month [No SAE] All AE's at low dose (&lt;2mg/kg) [No symptom. hypoglycemia]</td>
<td>0,0%</td>
<td>ND</td>
<td>Poor weight gain</td>
<td>Weight gain poor</td>
<td>1</td>
<td>2,86%</td>
<td>&lt;6 weeks</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben-Amotazed[2012]Israel</td>
<td>10</td>
<td>ECG, echocardo]BP HR BG for 3 days at hosp] Monthly FU [No abnormal findings BP HR BG</td>
<td>4</td>
<td>40,0%</td>
<td>Wheezing (no asthma history, airway obstruction due to IH)</td>
<td>Wheezing</td>
<td>1</td>
<td>10,00%</td>
<td>7-14 months</td>
<td>DD (no hosp)</td>
<td>Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blatt et al.[2011]USA</td>
<td>54</td>
<td>Bsl: ECG [if less than 3 months of age] 2 infants max dose: 4 or 5 mg/kg/d6 AE's moderate to severe] 5 AE's potentially life threatening</td>
<td>9</td>
<td>16,7%</td>
<td>Wheeze (mild)</td>
<td>Wheezing</td>
<td>1</td>
<td>1,85%</td>
<td>One month</td>
<td>None</td>
<td>No change of ADR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chak et al.[2010]Hong Kong</td>
<td>12</td>
<td>Hosp for 3 days]ECG, BP, BG]BP every hour for 3 hours]BG every day]Visit at W1 then every 4-6 weeks</td>
<td>3</td>
<td>25,0%</td>
<td>Wheezing</td>
<td>Wheezing</td>
<td>1</td>
<td>8,33%</td>
<td>ND</td>
<td>TD: tit interrupted for 4 months, salbutamol added</td>
<td>Resolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>Comments (Monitoring + Safety additional results)</td>
<td>N. patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N. patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
</tr>
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<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Graaf (de) et al</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td>Monitoring FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Wheezing</td>
<td>1</td>
<td>3,57%</td>
</tr>
<tr>
<td>Graaf (de) et al</td>
<td>2011</td>
<td>Netherlands</td>
<td>28</td>
<td>At risk in in-patient clinic (discharged on D5 or after 10 doses)</td>
<td>Bsl: ECG</td>
<td>Monitoring FU: 1, 2, 4, 8, 12 weeks</td>
<td>BP, HR</td>
<td>0,0%</td>
<td>ND</td>
<td>Bronchial hyperreactivity (wheezing, associated with viral inf. + no history of bronchial hyperreactivity)</td>
<td>Wheezing</td>
<td>2</td>
<td>7,14%</td>
</tr>
<tr>
<td>Hassan</td>
<td>2014</td>
<td>Egypt</td>
<td>30</td>
<td>Hosp 1 or 2 first days</td>
<td>ECG echocardo bsl Monitoring (BP, HR, BG)</td>
<td>2 D (D1, D2): 1 to 3 times a day (before and 2h after each dose)</td>
<td>FU: every 2 weeks (EGC BP HR)</td>
<td>No significant hypotension, hypoglycemia or bradycardia</td>
<td>0,0%</td>
<td>ND</td>
<td>Wheezy chest + Tachypnea</td>
<td>Wheezing</td>
<td>2</td>
</tr>
<tr>
<td>Hermans</td>
<td>2013</td>
<td>Netherlands</td>
<td>174</td>
<td>ECG (all pts) Echocardio (75 first pts)</td>
<td>Tt started at home</td>
<td>Day care sitting at the target dose start</td>
<td>FU every 6 weeks</td>
<td>108</td>
<td>62,1%</td>
<td>Wheezing during URTI</td>
<td>Wheezing</td>
<td>16</td>
<td>9,20%</td>
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<tr>
<td>Lynch</td>
<td>2014</td>
<td>Ireland</td>
<td>44</td>
<td>Hosp 48h for initiation</td>
<td>Bsl: HR, BP, temp., BG, ECG, echocardo</td>
<td>Monitoring for 8H at each dose increase: BP, HR: every 30 min for 4h, then hourly; BG 1h and 2h after each dose</td>
<td>FU weekly (BP HR)</td>
<td>AEts were mild in most patients</td>
<td>Other non documented AEts were mild: Gastrointestinal effects, Sleep disturbance, Cool peripheries</td>
<td>0,0%</td>
<td>ND</td>
<td>Wheeze associated with lower respiratory tract infection</td>
<td>Wheezing</td>
</tr>
<tr>
<td>Sagi</td>
<td>2014</td>
<td>Israel</td>
<td>99</td>
<td>Hosp for 3 days</td>
<td>ECG, echocardo before init.</td>
<td>Monitoring BP, HR, BG</td>
<td>Then BP, HR weekly</td>
<td>Decrease dose by half/mild side effects= wheezing, irritability or sleep disturbance</td>
<td>Discontinuation if SAE</td>
<td>32% of patients had mild side effects</td>
<td>32</td>
<td>32,3%</td>
<td>Recalcitrant dyspnea and wheezing</td>
</tr>
<tr>
<td>Sans et al</td>
<td>2009</td>
<td>France</td>
<td>32</td>
<td>ECG, echocardio</td>
<td>Short hosp 24h</td>
<td>Monitoring BP HR every h over 6 first h of tt</td>
<td>Evaluation after 10 days then monthly</td>
<td>Mild side effects</td>
<td>0,0%</td>
<td>ND</td>
<td>Wheeze (related to underlying allergic asthma)</td>
<td>Wheezing</td>
<td>1</td>
</tr>
<tr>
<td>Smit</td>
<td>2011</td>
<td>Israel</td>
<td>30</td>
<td>ECG echocardo</td>
<td>24h hosp with BP HR BG monitor.</td>
<td>+ after 1 week then every 6-8 weeks</td>
<td>No abnormal finding of BP HR and BG</td>
<td>DA in 3 patients</td>
<td>11</td>
<td>36,7%</td>
<td>Severe wheezing</td>
<td>Wheezing</td>
<td>1</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Country</td>
<td>N. Patients Treated with Propranolol</td>
<td>(Monitoring + Safety additional results)</td>
<td>N patients with any AE</td>
<td>(%) patients with any AE</td>
<td>Patients with any AE (other)</td>
<td>AE Notified</td>
<td>AE MedDRA preferred term</td>
<td>N patients with AE</td>
<td>(%) patients with AE</td>
<td>Time to AE onset</td>
<td>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/Def. disc. (DD)</td>
<td>Outcome: Resolved/Not documented (ND)/Death</td>
</tr>
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</tr>
<tr>
<td>Betlloch-Mas et al. [2012] Spain</td>
<td>20</td>
<td>ECG and echo, BP, HR, lab at bsl[BP, HR, BG, weight: 5h after 1st dose then twice monthly/1st month, then monthly][No hypoglycemia, hypotension, diarrhea, hypokalemia, respiratory difficulty</td>
<td>6</td>
<td>30,0%</td>
<td>Xerosis</td>
<td>Xerosis</td>
<td>1</td>
<td>5,00%</td>
<td>ND</td>
<td>None</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abarzua-Araya et al. [2014] Chile</td>
<td>10</td>
<td>At 48 to 72 hours after treatment start, patients evaluated by a pediatric cardiologist. 7 to 10 days after treatment initiation, evaluated by 24-hour ECG Holter. If HR or BP altered or any symptom present, treatment withdrawn and all patients were sent to a new evaluation with a pediatric cardiologist [Mean HR: 127.3 bpm (range 61-203 bpm), no difference between both drugs (P = .82). Asymptomatic.][Mean BP was 70.3 mm Hg (range 64-81 mm Hg) within normal range and no differences between groups (P = .2).</td>
<td>0</td>
<td>0,0%</td>
<td>0</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celik [2012] Turkey</td>
<td>67</td>
<td>Hosp first 24h; HR, BP, BG on D1 (1 and 3h post-dose)[Echocardiography and ECG at baseline, 1 and 6 months][Clin FU at 1, 3 and 6 months][No side effects and no abnormalities in BG, HR, BP, echocardiography and ECG during hosp and at control visits</td>
<td>0</td>
<td>0,0%</td>
<td>0</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng [2010] Australia</td>
<td>10</td>
<td>No side effects</td>
<td>0</td>
<td>0,0%</td>
<td>0</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cushing [2010] USA</td>
<td>44</td>
<td>39 outpatients, 5 inpatients[Cardio ev (ECG, echocardiography) at screening][BP, HR bsl, 1, 2h, 3h after init][No symptomatic hypotension, bradycardia or heart failure at starting dose][Max change in SBP and HR at 2h (absolute measures: SBP -7.2 mmHg at 2h, DBP -10.2 mmHg at 3h, HR -15.4 bpm at 2h)]</td>
<td>0</td>
<td>0,0%</td>
<td>0</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kagami [2013] Japan</td>
<td>15</td>
<td>Baseline ECG, echocardiography and Chest Rx[HR, BP, BG and clin FU every 2 weeks][No Hypoglycemia, hypotension or bradycardia occurred</td>
<td>0</td>
<td>0,0%</td>
<td>0</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadykov [2013] Germany [Uzbekistan] Canada</td>
<td>71</td>
<td>Before tt: cardio exam+ECG+BP[Then monthly FU (inc BP HR)][No symptomatic hypotension][Mean reduction for the lowest measurements by 7/10 mmHg for SBP/DBP, and by 18 bpm for HR with no symptoms][Very few and mild AEs that did not imply dose reduction or DD]</td>
<td>0,0%</td>
<td>ND</td>
<td>0,0%</td>
<td>0,0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Wheezing Total** | 29 | 0,77% |

**Xerosis Total** | 1 | 0,03% |
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N. Patients Treated with Propranolol</th>
<th>Comments (Monitoring + Safety additional results)</th>
<th>N patients with any AE (%)</th>
<th>Patients with any AE (other)</th>
<th>AE Notified</th>
<th>AE MedDRA preferred term</th>
<th>N patients with AE (%)</th>
<th>Time to AE onset</th>
<th>Measures taken: None/Dose adjustment (DA)/ Temp. disc (TD)/ Def. disc. (DD)</th>
<th>Outcome: Resolved/ Not documented (ND)/ Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellino</td>
<td>2013</td>
<td>Italy</td>
<td>68</td>
<td>Bsl: 24h Holter, ECG and neuro exam; Clinical FU weekly for the 1st month then monthly; Monthly ECG control; No cardiovascular effects</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiss</td>
<td>2011</td>
<td>USA</td>
<td>11</td>
<td>N/A</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaher</td>
<td>2011</td>
<td>Egypt</td>
<td>30</td>
<td>BP, HR every 30 min for 4h after each dose on D1; BG if clinically indicated; Clinical FU weekly for the 1st month, 2-weekly for 2nd month, then monthly; Echocardiogram, ECG and lab every 2 months</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
5. *Supplementary adverse event/effect tables*

**Table 1** Manufacturer pooled clinical trial data: summary of adverse events by system organ class, high level group terms and preferred term reported in all patients, by frequency (by dose of propranolol [V0400SB] or placebo whatever the regimen and on all propranolol)
Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIONS AND INFESTATIONS</td>
<td>103 (43.6%)</td>
<td>116 (58.0%)</td>
<td>138 (58.7%)</td>
<td>254 (58.4%)</td>
</tr>
<tr>
<td>INFECTIONS - PATHOGEN UNSPECIFIED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOSOPHARYNGITIS</td>
<td>91 (38.6%)</td>
<td>101 (50.5%)</td>
<td>123 (52.3%)</td>
<td>224 (51.5%)</td>
</tr>
<tr>
<td>UPPER RESPIRATORY TRACT INFECTION</td>
<td>19 (8.1%)</td>
<td>17 (8.5%)</td>
<td>28 (11.9%)</td>
<td>45 (10.3%)</td>
</tr>
<tr>
<td>BRONCHITIS</td>
<td>10 (4.2%)</td>
<td>11 (5.5%)</td>
<td>30 (12.8%)</td>
<td>41 (9.4%)</td>
</tr>
<tr>
<td>RHINITIS</td>
<td>11 (4.7%)</td>
<td>21 (10.5%)</td>
<td>11 (4.7%)</td>
<td>32 (7.4%)</td>
</tr>
<tr>
<td>GASTROENTERITIS</td>
<td>4 (1.7%)</td>
<td>7 (3.5%)</td>
<td>18 (7.7%)</td>
<td>25 (5.7%)</td>
</tr>
<tr>
<td>EAR INFECTION</td>
<td>8 (3.4%)</td>
<td>10 (5.0%)</td>
<td>9 (3.8%)</td>
<td>19 (4.4%)</td>
</tr>
<tr>
<td>PHARYNGITIS</td>
<td>4 (1.7%)</td>
<td>5 (2.5%)</td>
<td>4 (1.7%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>OTITIS MEDIA</td>
<td>4 (1.7%)</td>
<td>1 (0.5%)</td>
<td>3 (1.3%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>RESPIRATORY TRACT INFECTION</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>2 (0.9%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>TRACHEITIS</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>2 (0.9%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>LARYNGITIS</td>
<td>5 (2.1%)</td>
<td>2 (1.0%)</td>
<td>1 (0.4%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>FEBRILE INFECTION</td>
<td>2 (0.8%)</td>
<td>2 (1.0%)</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>ACUTE TONSILLITIS</td>
<td>-</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>CYSTITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>LOWER RESPIRATORY TRACT INFECTION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>URINARY TRACT INFECTION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>CONJUNCTIVITIS INFECTIVE</td>
<td>2 (0.8%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>EYE INFECTION</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>OTITIS MEDIA ACUTE</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>TONSILLITIS</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>BRONCHOPNEUMONIA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ENTERITIS INFECTIOUS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>INFECTED BITES</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>OTITIS EXTERNA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PHARYNGOTONSILLITIS</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PNEUMONIA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PYELONEPHRITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SUBCUTANEOUS ABSCESS</td>
<td>-</td>
<td>1 (0.5%)</td>
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</tr>
<tr>
<td>TRACHEOBRONCHITIS</td>
<td>-</td>
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<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>VIRAEMIA</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>DACRYOCYSTITIS</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
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</tr>
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</table>

(1/14 (CONTINUED))
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
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<tbody>
<tr>
<td>INFECTIONS AND INFESTATIONS (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFECTION - PATHOGEN UNSPECIFIED (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFECTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RASH PUSTULAR</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VIRAL INFECTIOUS DISORDERS</td>
<td>19 (8.1%)</td>
<td>30 (15.0%)</td>
<td>36 (15.3%)</td>
<td>66 (15.2%)</td>
</tr>
<tr>
<td>BRONCHIOLITIS</td>
<td>10 (4.2%)</td>
<td>11 (5.5%)</td>
<td>16 (6.8%)</td>
<td>27 (6.2%)</td>
</tr>
<tr>
<td>INFLUENZA</td>
<td>2 (0.8%)</td>
<td>4 (2.0%)</td>
<td>7 (3.0%)</td>
<td>11 (2.5%)</td>
</tr>
<tr>
<td>VIRAL UPPER RESPIRATORY TRACT INFECTION</td>
<td>2 (0.8%)</td>
<td>5 (2.5%)</td>
<td>4 (1.7%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>VIRAL INFECTION</td>
<td>-</td>
<td>5 (2.5%)</td>
<td>4 (1.7%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>RESPIRATORY TRACT INFECTION VIRAL</td>
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<td>5 (1.1%)</td>
</tr>
<tr>
<td>CROUP INFECTIOUS</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>CYTOMEGALOVIRUS INFECTION</td>
<td>-</td>
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<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>VARICELLA</td>
<td>-</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>EXANTHEMA SUBITUM</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
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</tr>
<tr>
<td>GASTROENTERITIS VIRAL</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>GASTROINTESTINAL INFECTION</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>ORAL HERPES</td>
<td>-</td>
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</tr>
<tr>
<td>RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS</td>
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</tr>
<tr>
<td>RESPIRATORY SYNCYTIAL VIRUS INFECTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ROTAVIRUS INFECTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FUNGAL INFECTIOUS DISORDERS</td>
<td>4 (1.7%)</td>
<td>7 (3.5%)</td>
<td>6 (2.6%)</td>
<td>13 (3.0%)</td>
</tr>
<tr>
<td>ORAL CANDIDIASIS</td>
<td>-</td>
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<td>2 (0.9%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>CANDIDIASIS</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>FUNGAL INFECTION</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>FUNGAL SKIN INFECTION</td>
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<td>2 (0.5%)</td>
</tr>
<tr>
<td>CANDIDA NAPPY RASH</td>
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<td>1 (0.5%)</td>
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<td>2 (0.5%)</td>
</tr>
<tr>
<td>ORAL FUNGAL INFECTION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>VULVOVAGINAL MYCOTIC INFECTION</td>
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</tr>
<tr>
<td>TINEA PEDIS</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BACTERIAL INFECTIOUS DISORDERS</td>
<td>2 (0.8%)</td>
<td>1 (0.5%)</td>
<td>2 (0.9%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>CONJUNCTIVITIS BACTERIAL</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>CAMPYLOBACTER GASTROENTERITIS</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>PERTUSSIS</td>
<td>2 (0.8%)</td>
<td>-</td>
<td>-</td>
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</tr>
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</table>

2/14 (CONTINUED)
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>High Level Group Term</th>
<th>Preferred Term</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTIONS AND INFESTATIONS (Continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANGILLARY INFECTIOUS TOPICS</td>
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</tr>
<tr>
<td>ROSEOLA</td>
<td>2 (0.8%)</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
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</tr>
<tr>
<td>ECTOPARASITIC DISORDERS</td>
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<td>1 (0.4%)</td>
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</tr>
<tr>
<td>ACARODERMATITIS</td>
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</tr>
<tr>
<td>HELMINTHIC DISORDERS</td>
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<td>-</td>
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<td></td>
</tr>
<tr>
<td>HELMINTHIC INFECTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS</td>
<td>56 (23.7%)</td>
<td>102 (51.0%)</td>
<td>123 (52.3%)</td>
<td>225 (51.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIARRHOEA</td>
<td>14 (5.9%)</td>
<td>47 (23.5%)</td>
<td>70 (29.8%)</td>
<td>117 (26.9%)</td>
<td></td>
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</tr>
<tr>
<td>CONSTIPATION</td>
<td>9 (3.8%)</td>
<td>29 (14.5%)</td>
<td>53 (22.6%)</td>
<td>82 (18.9%)</td>
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<td></td>
</tr>
<tr>
<td>GASTROESOPHAGEAL REFLUX DISEASE</td>
<td>3 (1.3%)</td>
<td>14 (7.0%)</td>
<td>15 (6.4%)</td>
<td>29 (6.7%)</td>
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</tr>
<tr>
<td>FREQUENT BOWEL MOVEMENTS</td>
<td>1 (0.4%)</td>
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<td>7 (3.0%)</td>
<td>11 (2.5%)</td>
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<tr>
<td>DENTAL AND GINGIVAL CONDITIONS</td>
<td>34 (14.4%)</td>
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<td>55 (23.4%)</td>
<td>99 (22.8%)</td>
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<td>32 (13.6%)</td>
<td>68 (15.6%)</td>
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<tr>
<td>TOOTHACHE</td>
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<td>21 (8.9%)</td>
<td>27 (6.2%)</td>
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<tr>
<td>GINGIVAL PAIN</td>
<td>4 (1.7%)</td>
<td>2 (1.0%)</td>
<td>7 (3.0%)</td>
<td>9 (2.1%)</td>
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<tr>
<td>GASTROINTESTINAL SIGNS AND SYMPTOMS</td>
<td>20 (8.5%)</td>
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<td>97 (22.3%)</td>
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<td>YOMITING</td>
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<tr>
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<td>14 (3.2%)</td>
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<td></td>
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<tr>
<td>FLATULENCE</td>
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<td>8 (4.0%)</td>
<td>5 (2.1%)</td>
<td>13 (3.0%)</td>
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</tr>
<tr>
<td>ABDOMINAL PAIN</td>
<td>1 (0.4%)</td>
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<td>5 (2.1%)</td>
<td>10 (2.3%)</td>
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</tr>
<tr>
<td>REGURGITATION</td>
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<td>6 (1.4%)</td>
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<td>4 (0.9%)</td>
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</tr>
<tr>
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<td>3 (0.7%)</td>
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<tr>
<td>FAECES DISCOLOURED</td>
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<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
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<tr>
<td>ABNORMAL FAECES</td>
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<td>-</td>
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<td></td>
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<td>DYSPEPSIA</td>
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<tr>
<td>ABDOMINAL PAIN UPPER</td>
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<tr>
<td>AEROPHAGIA</td>
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<tr>
<td>MUCOUS STOOLS</td>
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<td>-</td>
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<td>NAUSEA</td>
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</table>

(Continued)
## Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo</th>
<th>All V0400SB 1mg/kg/day</th>
<th>All V0400SB 3mg/kg/day</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS (Continued)</strong></td>
<td>All Placebo n=236</td>
<td>All V0400SB 1mg/kg/day</td>
<td>All V0400SB 3mg/kg/day</td>
<td>All V0400SB n=435</td>
</tr>
<tr>
<td>GASTROINTESTINAL INFLAMMATORY CONDITIONS</td>
<td>All Placebo</td>
<td>All V0400SB 1mg/kg/day</td>
<td>All V0400SB 3mg/kg/day</td>
<td>All V0400SB n=435</td>
</tr>
<tr>
<td>ENTERITIS</td>
<td>-</td>
<td>2 (1.0%)</td>
<td>4 (1.7%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>ENTEROCOLITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>GASTRITIS</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>OESOPHAGITIS</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>PROCTITIS HAEMORRHAGIC</td>
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<td>-</td>
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</tr>
<tr>
<td>ORAL SOFT TISSUE CONDITIONS</td>
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<td>All V0400SB 3mg/kg/day</td>
<td>All V0400SB n=435</td>
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<tr>
<td>ENTERITIS</td>
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<td>1 (0.4%)</td>
<td>3 (0.7%)</td>
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<tr>
<td>ENTEROCOLITIS</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>GASTRITIS</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>OESOPHAGITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ORAL PAIN</td>
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<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ODYNOPHAGIA</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>ORAL PAIN</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ODYNOPHAGIA</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>GASTROINTESTINAL STENOSIS AND OBSTRUCTION</td>
<td>All Placebo</td>
<td>All V0400SB 1mg/kg/day</td>
<td>All V0400SB 3mg/kg/day</td>
<td>All V0400SB n=435</td>
</tr>
<tr>
<td>ENTERITIS</td>
<td>-</td>
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<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ENTEROCOLITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>GASTRITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>OESOPHAGITIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>TONGUE CONDITIONS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>TONGUE DISCOLOURATION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td>All Placebo</td>
<td>All V0400SB 1mg/kg/day</td>
<td>All V0400SB 3mg/kg/day</td>
<td>All V0400SB n=435</td>
</tr>
<tr>
<td>BODY TEMPERATURE CONDITIONS</td>
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<td>44 (22.0%)</td>
<td>53 (22.6%)</td>
<td>97 (22.3%)</td>
</tr>
<tr>
<td>PYREXIA</td>
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<td>44 (22.0%)</td>
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<td>97 (22.3%)</td>
</tr>
<tr>
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<td>12 (5.1%)</td>
<td>25 (12.5%)</td>
<td>16 (6.8%)</td>
<td>41 (9.4%)</td>
</tr>
<tr>
<td>IRRITABILITY</td>
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<td>11 (5.5%)</td>
<td>3 (1.3%)</td>
<td>14 (3.2%)</td>
</tr>
<tr>
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<td>-</td>
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<td>3 (1.3%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>CONDITION AGGRAVATED</td>
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<td>4 (1.7%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>FATIGUE</td>
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<td>3 (1.5%)</td>
<td>1 (0.4%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>DISCOMFORT</td>
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<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
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<tr>
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<td>OEDEMA</td>
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<td>ASTHENIA</td>
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<td>1 (0.2%)</td>
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<td>FEELING COLD</td>
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<td>-</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>High Level Group Term</th>
<th>Preferred Term</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
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<tbody>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong> (Continued)</td>
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<tr>
<td>GENERAL SYSTEM DISORDERS NEC (Continued)</td>
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<td>IRRITABILITY POSTVACCINAL</td>
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<tr>
<td>ADMINISTRATION SITE REACTIONS</td>
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<td>5 (1.1%)</td>
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<tr>
<td>VACCINATION SITE PAIN</td>
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<td>3 (1.3%)</td>
<td>4 (0.9%)</td>
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<tr>
<td>APPLICATION SITE PAIN</td>
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<tr>
<td>VACCINATION SITE REACTION</td>
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<td>-</td>
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<td>THERAPEUTIC AND NONTHERAPEUTIC EFFECTS (EXCL TOXICITY)</td>
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<td>DRUG INEFFECTIVE</td>
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<td>ADVERSE DRUG REACTION</td>
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<tr>
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<td>21 (8.9%)</td>
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<tr>
<td>SLEEP DISORDERS AND DISTURBANCES</td>
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<td>MIDDLE INSOMNIA</td>
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<tr>
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<tr>
<td>INSOMNIA</td>
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<tr>
<td>INITIAL INSOMNIA</td>
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<tr>
<td>TERMINAL INSOMNIA</td>
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<td>ANXIETY DISORDERS AND SYMPTOMS</td>
<td>3 (1.3%)</td>
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<tr>
<td>AGITATION</td>
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</tr>
<tr>
<td>NERVOUSNESS</td>
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<td>3 (1.3%)</td>
<td>4 (0.9%)</td>
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</tr>
<tr>
<td>ANXIETY</td>
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<td>4 (0.9%)</td>
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<tr>
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<tr>
<td>CHANGES IN PHYSICAL ACTIVITY</td>
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<tr>
<td>RESTLESSNESS</td>
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<td>3 (1.3%)</td>
<td>11 (2.5%)</td>
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</tr>
<tr>
<td>MOOD DISORDERS AND DISTURBANCES NEC</td>
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<tr>
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<td>2 (0.5%)</td>
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<tr>
<td>MOOD ALTERED</td>
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<td>-</td>
<td>-</td>
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</table>

5/14 (CONTINUED)
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCHIATRIC DISORDERS (Continued)</strong></td>
<td>All Placebo n=236</td>
<td>All V0400SB 1mg/kg/day n=200</td>
<td>All V0400SB 3mg/kg/day n=235</td>
<td>All V0400SB n=435</td>
</tr>
<tr>
<td>DELIRIA (INCL. CONFUSION)</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>CONFUSIONAL STATE</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>DEVELOPMENTAL DISORDERS NEC</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>NEURODEVELOPMENTAL DISORDER</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>EATING DISORDERS AND DISTURBANCES</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>FOOD AVERSION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PSYCHIATRIC AND BEHAVIOURAL SYMPTOMS NEC</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>STARING</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</strong></td>
<td>28 (11.9%)</td>
<td>41 (20.5%)</td>
<td>52 (22.1%)</td>
<td>93 (21.4%)</td>
</tr>
<tr>
<td>RESPIRATORY DISORDERS NEC</td>
<td>23 (9.7%)</td>
<td>35 (17.5%)</td>
<td>42 (19.9%)</td>
<td>77 (17.7%)</td>
</tr>
<tr>
<td>COUGH</td>
<td>17 (7.2%)</td>
<td>28 (14.0%)</td>
<td>28 (11.9%)</td>
<td>56 (12.9%)</td>
</tr>
<tr>
<td>RINO RHINORRHOEA</td>
<td>9 (3.8%)</td>
<td>5 (2.5%)</td>
<td>8 (3.4%)</td>
<td>13 (3.0%)</td>
</tr>
<tr>
<td>INCREASED BRONCHIAL SECRETION</td>
<td>-</td>
<td>1 (0.5%)</td>
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<td>3 (0.7%)</td>
</tr>
<tr>
<td>DYSPNOEA</td>
<td>-</td>
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<td>2 (0.5%)</td>
</tr>
<tr>
<td>PRODUCTIVE COUGH</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>RESPIRATORY TRACT CONGESTION</td>
<td>-</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>OROPHARYNGEAL PAIN</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>APNOEA</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>LUNG DISORDER</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SNEEZING</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SNORING</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>THROAT LESION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>UPPER AIRWAY OBSTRUCTION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
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</tr>
<tr>
<td>UPPER RESPIRATORY TRACT INFLAMMATION</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>NASAL OBSTRUCTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>THROAT IRRITATION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UPPER RESPIRATORY TRACT DISORDERS (EXCL INFECTIONS)</td>
<td>3 (1.3%)</td>
<td>10 (5.0%)</td>
<td>8 (3.4%)</td>
<td>18 (4.1%)</td>
</tr>
<tr>
<td>NASAL CONGESTION</td>
<td>3 (1.3%)</td>
<td>8 (4.0%)</td>
<td>7 (3.0%)</td>
<td>15 (3.4%)</td>
</tr>
<tr>
<td>EPISTAXIS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>PHARYNGEAL ODEMA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>BRONCHIAL DISORDERS (EXCL NEOPLASMS)</td>
<td>4 (1.7%)</td>
<td>2 (1.0%)</td>
<td>6 (2.6%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>ASTHMA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>3 (1.3%)</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>

---

(Continued)
### Summary of Clinical Safety

#### Number of Patients with at Least One TEAE, by SOC, HLGT, PT, by Dose of V0400SB or Placebo Whatever the Regimen and on All V0400SB [Safety Set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo</th>
<th>All V0400SB 1mg/kg/day</th>
<th>All V0400SB 3mg/kg/day</th>
<th>All V0400SB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=236</td>
<td>n=200</td>
<td>n=235</td>
<td>n=435</td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRONCHIAL DISORDERS (EXCL NEOPLASMS) (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRONCHOSPASM</td>
<td>2 (0.8%)</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>BRONCHIAL HYPERREACTIVITY</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>OBSTRUCTIVE AIRWAYS DISORDER</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>BRONCHIAL OBSTRUCTION</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHEEZING</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LOWER RESPIRATORY TRACT DISORDERS (EXCL OBSTRUCTION AND INFECTION)</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>PULMONARY CONGESTION</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td>18 (7.6%)</td>
<td>42 (21.0%)</td>
<td>44 (18.7%)</td>
<td>86 (19.8%)</td>
</tr>
<tr>
<td>EPIDERMAL AND DERMAL CONDITIONS</td>
<td>17 (7.2%)</td>
<td>36 (18.0%)</td>
<td>37 (15.7%)</td>
<td>73 (16.8%)</td>
</tr>
<tr>
<td>DERMATITIS DIAPER</td>
<td>3 (1.3%)</td>
<td>9 (4.5%)</td>
<td>12 (5.1%)</td>
<td>21 (4.8%)</td>
</tr>
<tr>
<td>ECZEMA</td>
<td>3 (1.3%)</td>
<td>10 (5.0%)</td>
<td>5 (2.1%)</td>
<td>15 (3.4%)</td>
</tr>
<tr>
<td>RASH</td>
<td>4 (1.7%)</td>
<td>5 (2.5%)</td>
<td>7 (3.0%)</td>
<td>12 (2.8%)</td>
</tr>
<tr>
<td>ERYTHEMA</td>
<td>1 (0.4%)</td>
<td>3 (1.5%)</td>
<td>5 (2.1%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>DERMATITIS ATOPIC</td>
<td>2 (0.8%)</td>
<td>3 (1.5%)</td>
<td>3 (1.3%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>DRY SKIN</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>3 (1.5%)</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>SEBORRHOEIC DERMATITIS</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>3 (1.3%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>DERMATITIS</td>
<td>-</td>
<td>2 (1.0%)</td>
<td>1 (0.4%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>DERMATITIS CONTACT</td>
<td>-</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>INTERTRIGO</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>SKIN DISCOLOURATION</td>
<td>-</td>
<td>-</td>
<td>2 (0.9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>DERMATITIS ALLERGIC</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>MACULE</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PAPULE</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ECZEMA NUMMULAR</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>PRURIGO</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>RASH ERYTHEMATOUS</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN FISSURES</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN IRRITATION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN LESION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN APPENDAGE CONDITIONS</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>7 (3.0%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>ALOPECIA</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>2 (0.9%)</td>
<td>3 (0.7%)</td>
</tr>
</tbody>
</table>
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKIN APPENDAGE CONDITIONS (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COLD SWEAT</td>
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<td>-</td>
<td>3 (1.3%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>HYPERHIDROSIS</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ACNE</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN VASCULAR ABNORMALITIES</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>3 (1.3%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>PETECHIAE</td>
<td>-</td>
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<td>2 (0.9%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>VASCULAR SKIN DISORDER</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>TELANGIECTASIA</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>ANGIOEDEMA AND URTICARIA</td>
<td>-</td>
<td>3 (1.5%)</td>
<td>-</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>URTICARIA</td>
<td>-</td>
<td>3 (1.5%)</td>
<td>-</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</td>
<td>6 (2.5%)</td>
<td>21 (10.5%)</td>
<td>20 (8.5%)</td>
<td>41 (9.4%)</td>
</tr>
<tr>
<td>PROCEDURAL RELATED INJURIES AND COMPLICATIONS NEC VACCINATION COMPLICATION</td>
<td>2 (0.8%)</td>
<td>16 (8.0%)</td>
<td>16 (6.8%)</td>
<td>32 (7.4%)</td>
</tr>
<tr>
<td>INJURIES NEC</td>
<td>3 (1.3%)</td>
<td>3 (1.5%)</td>
<td>5 (2.1%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>FALL</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>-</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>ARTHROPOD BITE</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>ARTHROPOD STING</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>BITE</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>CRANIOCEREBRAL INJURY</td>
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</tr>
<tr>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>HEAD INJURY</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>MOUTH INJURY</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEDICATION ERRORS</td>
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<td>2 (1.0%)</td>
<td>-</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>OVERDOSE</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>DRUG DOSE OMISION</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>INJURIES BY PHYSICAL AGENTS</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>THERMAL BURN</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>VASCULAR DISORDERS</td>
<td>3 (1.3%)</td>
<td>21 (10.5%)</td>
<td>20 (8.5%)</td>
<td>41 (9.4%)</td>
</tr>
<tr>
<td>ARTERIOSCLEROSIS, STENOSIS, VASCULAR INSUFFICIENCY AND NECROSIS</td>
<td>1 (0.4%)</td>
<td>18 (9.0%)</td>
<td>15 (6.4%)</td>
<td>33 (7.6%)</td>
</tr>
<tr>
<td>PERIPHERAL COLDNESS</td>
<td>1 (0.4%)</td>
<td>18 (9.0%)</td>
<td>15 (6.4%)</td>
<td>33 (7.6%)</td>
</tr>
</tbody>
</table>
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VASCULAR DISORDERS (Continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased and Nonspecific Blood Pressure Disorders and Shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (0.4%)</td>
<td>3 (1.5%)</td>
<td>4 (1.7%)</td>
<td>7 (1.6%)</td>
</tr>
<tr>
<td>Diastolic Hypotension</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Vascular Haemorrhagic Disorders</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Haematoma</td>
<td>-</td>
<td>1 (0.4%)</td>
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<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Vascular Disorders NEC</td>
<td>-</td>
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<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Pallor</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM DISORDERS</strong></td>
<td>5 (2.1%)</td>
<td>24 (12.0%)</td>
<td>12 (5.1%)</td>
<td>36 (8.3%)</td>
</tr>
<tr>
<td>Sleep Disturbances (Incl Subtypes)</td>
<td>2 (0.8%)</td>
<td>6 (3.0%)</td>
<td>9 (3.8%)</td>
<td>17 (3.9%)</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1 (0.4%)</td>
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<td>5 (2.1%)</td>
<td>11 (2.5%)</td>
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<tr>
<td>Poor Quality Sleep</td>
<td>1 (0.4%)</td>
<td>3 (1.5%)</td>
<td>4 (1.7%)</td>
<td>7 (1.6%)</td>
</tr>
<tr>
<td>Neurological Disorders NEC</td>
<td>1 (0.4%)</td>
<td>10 (5.0%)</td>
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<td>13 (3.0%)</td>
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<tr>
<td>Somnolence</td>
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<td>12 (2.8%)</td>
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<tr>
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<tr>
<td>Movement Disorders (Incl Parkinsonism)</td>
<td>-</td>
<td>5 (2.5%)</td>
<td>1 (0.4%)</td>
<td>6 (1.4%)</td>
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<tr>
<td>Psychomotor Hyperactivity</td>
<td>-</td>
<td>2 (1.0%)</td>
<td>1 (0.4%)</td>
<td>3 (0.7%)</td>
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<tr>
<td>Dyskinesia</td>
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<td>Head Titubation</td>
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<td>1 (0.2%)</td>
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<tr>
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</tr>
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<td>Hypertonia</td>
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<td>Seizures (Incl Subtypes)</td>
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<td>Epilepsy</td>
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<td>1 (0.2%)</td>
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<td>Convulsion</td>
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<td>Cranial Nerve Disorders (Excl Neoplasms)</td>
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<td>19 (8.1%)</td>
<td>33 (7.6%)</td>
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<tr>
<td>Ocular Infections, Irritations and Inflammations</td>
<td>5 (2.1%)</td>
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<td>17 (7.2%)</td>
<td>30 (6.9%)</td>
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<td>Conjunctivitis</td>
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<td>11 (5.5%)</td>
<td>15 (6.4%)</td>
<td>26 (6.0%)</td>
</tr>
</tbody>
</table>
Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
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<tr>
<td><strong>EYE DISORDERS</strong></td>
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<tr>
<td>(Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Infections, Irritations and Inflammations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EYE DISCHARGE</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
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<td>OCULAR HYPERAEMIA</td>
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<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
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<td>ERYTHEMA OF EYELID</td>
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<td>1 (0.2%)</td>
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<td>1 (0.2%)</td>
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<td>ULCERATIVE KERATITIS</td>
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<td>1 (0.4%)</td>
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<td>2 (0.5%)</td>
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<td>1 (0.2%)</td>
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<td>EXCESSIVE EYE BLINKING</td>
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</tr>
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<td>STRABISMUS</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VISION DISORDERS</td>
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<td>1 (0.4%)</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>ASTIGMATISM</td>
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<td><strong>INVESTIGATIONS</strong></td>
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<tr>
<td></td>
<td>7 (3.0%)</td>
<td>14 (7.0%)</td>
<td>16 (6.8%)</td>
<td>30 (6.9%)</td>
</tr>
<tr>
<td>Haematology Infections (Incl Blood Groups)</td>
<td>1 (0.4%)</td>
<td>7 (3.5%)</td>
<td>1 (0.4%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>Neutrophil Count Decreased</td>
<td>-</td>
<td>2 (1.0%)</td>
<td>-</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Neutrophil Count Abnormal</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Basophil Count Increased</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Eosinophil Count Increased</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Mean Cell Volume Abnormal</td>
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<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
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<tr>
<td>Platelet Count Increased</td>
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<td>1 (0.2%)</td>
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<tr>
<td>White Blood Cell Count Increased</td>
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<td>1 (0.5%)</td>
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<td>1 (0.2%)</td>
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<tr>
<td>Water, Electrolyte and Mineral Investigations</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>6 (2.6%)</td>
<td>8 (1.8%)</td>
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<tr>
<td>Blood Potassium Increased</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>3 (1.3%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>Blood Calcium Increased</td>
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<td>2 (0.9%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Blood Iron Decreased</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Hepatobiliary Investigations</td>
<td>2 (0.8%)</td>
<td>2 (1.0%)</td>
<td>4 (1.7%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increased</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>3 (1.3%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Alanine Aminotransferase Increased</td>
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<td>2 (0.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Transaminases Increased</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Cardiac and Vascular Investigations (Excl Enzyme Tests)</td>
<td>2 (0.8%)</td>
<td>3 (1.5%)</td>
<td>2 (0.9%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Electrocardiogram QT Prolonged</td>
<td>1 (0.4%)</td>
<td>2 (1.0%)</td>
<td>1 (0.4%)</td>
<td>3 (0.7%)</td>
</tr>
</tbody>
</table>
## Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INVESTIGATIONS (Continued)</strong></td>
<td></td>
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<tr>
<td>CARDIAC AND VASCULAR INVESTIGATIONS (EXCL ENZYME TESTS) (Continued)</td>
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<tr>
<td>CARDIAC MURMUR</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>-</td>
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<tr>
<td>ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PHYSICAL EXAMINATION AND ORGAN SYSTEM STATUS TOPICS</td>
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<tr>
<td>WEIGHT DECREASED</td>
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<td>3 (0.7%)</td>
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<td>ENZYME INVESTIGATIONS NEC</td>
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<tr>
<td>BLOOD ALKALINE PHOSPHATASE INCREASED</td>
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<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
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<tr>
<td>IMMUNOLOGY AND ALLERGY INVESTIGATIONS</td>
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<td>BLOOD IMMUNOGLOBULIN E INCREASED</td>
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<td>1 (0.5%)</td>
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<td>METABOLIC, NUTRITIONAL AND BLOOD GAS INVESTIGATIONS</td>
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<td>URINE CALCIUM/CREATININE RATIO INCREASED</td>
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<td>PROTEIN AND CHEMISTRY ANALYSES NEC</td>
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<td>PROTEIN TOTAL DECREASED</td>
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</tr>
<tr>
<td>RENAL AND URINARY TRACT INVESTIGATIONS AND URINALYSES</td>
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<tr>
<td>BLOOD CREATININE INCREASED</td>
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<td>1 (0.2%)</td>
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<td>NEUROLOGICAL, SPECIAL SENSES AND PSYCHIATRIC INVESTIGATIONS</td>
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<td>VISUAL ACUITY TESTS</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td>6 (2.5%)</td>
<td>14 (7.0%)</td>
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<td>26 (6.0%)</td>
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<tr>
<td>APPETITE AND GENERAL NUTRITIONAL DISORDERS</td>
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<td>17 (3.9%)</td>
</tr>
<tr>
<td>FEEDING DISORDER</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>INCREASED APPETITE</td>
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<td>2 (0.5%)</td>
</tr>
<tr>
<td>WEIGHT GAIN POOR</td>
<td>3 (1.3%)</td>
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<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
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<tr>
<td>FEEDING DISORDER NEONATAL</td>
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<td>1 (0.5%)</td>
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<td>ELECTROLYTE AND FLUID BALANCE CONDITIONS</td>
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<td>POLYDIPSIA</td>
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<td>DEHYDRATION</td>
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<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

(Continued)
### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo</th>
<th>All V0400SB 1mg/kg/day</th>
<th>All V0400SB 3mg/kg/day</th>
<th>All V0400SB 5mg/kg/day</th>
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<td>n=200</td>
<td>n=235</td>
<td>n=435</td>
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<td>METABOLISM DISORDERS NEC</td>
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<td>HYPERPHOSPHATASEMIA</td>
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<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
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<td>1 (0.2%)</td>
</tr>
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<td><strong>SPLEEN, LYMPHATIC AND RETICULOENDOTHELIAL SYSTEM</strong></td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
<td>-</td>
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<td>3 (1.3%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
<td>-</td>
<td>3 (1.5%)</td>
<td>2 (0.9%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>MUSCULOSKELETAL STIFFNESS</td>
<td>-</td>
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<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
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<tr>
<td>POSTURE ABNORMAL</td>
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<td>1 (0.2%)</td>
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<tr>
<td><strong>BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)</strong></td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>MUSCLE DISORDERS</strong></td>
<td>-</td>
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<td>1 (0.2%)</td>
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<tr>
<td><strong>MUSCULAR WEAKNESS</strong></td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
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### Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAR AND LABYRINTH DISORDERS</td>
<td>2 (0.8%)</td>
<td>2 (0.9%)</td>
<td>3 (0.7%)</td>
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<tr>
<td>AURAL DISORDERS NEC</td>
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<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
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<tr>
<td>EAR HAEMORRHAGE</td>
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<td>EAR DISORDER</td>
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<td>EXTERNAL EAR DISORDERS (EXCL CONGENITAL)</td>
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<td>HEARING DISORDERS</td>
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<td>-</td>
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<td>HYPOACUSIS</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>SURGICAL AND MEDICAL PROCEDURES</td>
<td>1 (0.4%)</td>
<td>3 (1.5%)</td>
<td>-</td>
<td>3 (0.7%)</td>
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<tr>
<td>EYE THERAPEUTIC PROCEDURES</td>
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</tr>
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<td>CATARACT OPERATION</td>
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<td>GASTROINTESTINAL THERAPEUTIC PROCEDURES</td>
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<tr>
<td>ILEOSTOMY CLOSURE</td>
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<td>1 (0.5%)</td>
<td>-</td>
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</tr>
<tr>
<td>INGUINAL HERNIA REPAIR</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE THERAPEUTIC PROCEDURES</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>DERMABRASION</td>
<td>-</td>
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<td>-</td>
<td>1 (0.2%)</td>
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<tr>
<td>HEAD AND NECK THERAPEUTIC PROCEDURES</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>REMOVAL OF FOREIGN BODY FROM NOSE</td>
<td>1 (0.4%)</td>
<td>2 (0.9%)</td>
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<tr>
<td>IMMUNE SYSTEM DISORDERS</td>
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<td>ALLERGIC CONDITIONS</td>
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<td>ALLERGY TO ARTHROPOD STING</td>
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<td>-</td>
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<tr>
<td>FOOD ALLERGY</td>
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<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>IMMUNE DISORDERS NEC</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>IMMUNISATION REACTION</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>RENAL AND URINARY DISORDERS</td>
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<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
</tr>
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<td>RENAL DISORDERS (EXCL NEPHROPATHIES)</td>
<td>-</td>
<td>-</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>1 (0.2%)</td>
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<tr>
<td>URINARY TRACT SIGNS AND SYMPTOMS</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>URINE ODOUR ABNORMAL</td>
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<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>HEPATOBILIARY DISORDERS</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>HEPATIC AND HEPATOBILIARY DISORDERS</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>HEPATOCELLULAR INJURY</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
<td>1 (0.2%)</td>
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(13/14 CONTINUED)
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Placebo n=236</th>
<th>All V0400SB 1mg/kg/day n=200</th>
<th>All V0400SB 3mg/kg/day n=235</th>
<th>All V0400SB n=435</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.2%)</td>
<td></td>
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<tr>
<td>NEUROLOGICAL AND MUSCULOSKELETAL DISORDERS</td>
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<td>1 (0.5%)</td>
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<tr>
<td>MELANOCYTIC NAEVUS</td>
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<td>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</td>
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<td></td>
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<tr>
<td>BIRTH DEFECTS</td>
<td>-</td>
<td>1 (0.5%)</td>
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<tr>
<td>SOCIETAL, ECONOMICAL AND COMMUNITY ISSUES</td>
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<td></td>
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<td>-</td>
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<td>1 (0.2%)</td>
<td></td>
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<tr>
<td>LIFESTYLE ISSUES</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.2%)</td>
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</tr>
<tr>
<td>REFUSAL OF TREATMENT BY PATIENT</td>
<td>-</td>
<td>1 (0.5%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>CONGENITAL, FAMILIAL AND GENETIC DISORDERS</td>
<td>2 (0.8%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>EYE DISORDERS CONGENITAL</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DACRYOSTENOSIS CONGENITAL</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS CONGENITAL</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NAEVUS FLAMMEUS</td>
<td>1 (0.4%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Number of Patients with at Least one TEAE, by SOC, HLGT, PT, by dose of V0400SB or placebo whatever the regimen and on all V0400SB [Safety set]
<table>
<thead>
<tr>
<th>Preferred term</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE*</td>
<td>161</td>
<td>(9.7%)</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>38</td>
<td>(2.29%)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>19</td>
<td>(1.14%)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>13</td>
<td>(0.78%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>8</td>
<td>(0.48%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8</td>
<td>(0.48%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>(0.42%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>7</td>
<td>(0.42%)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>6</td>
<td>(0.36%)</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
<td>(0.36%)</td>
</tr>
<tr>
<td>Middle insomnia</td>
<td>6</td>
<td>(0.36%)</td>
</tr>
<tr>
<td>Peripheral coldness</td>
<td>6</td>
<td>(0.36%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>(0.30%)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>5</td>
<td>(0.30%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>5</td>
<td>(0.30%)</td>
</tr>
<tr>
<td>Pallor</td>
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<td>(0.30%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4</td>
<td>(0.24%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>(0.24%)</td>
</tr>
<tr>
<td>Weight gain poor</td>
<td>4</td>
<td>(0.24%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
<td>(0.18%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3</td>
<td>(0.18%)</td>
</tr>
<tr>
<td>Crying</td>
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<td>(0.18%)</td>
</tr>
<tr>
<td>Medication error</td>
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<td>(0.18%)</td>
</tr>
<tr>
<td>Raynaud’s syndrome</td>
<td>3</td>
<td>(0.18%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>(0.18%)</td>
</tr>
<tr>
<td>Vasoconstriction</td>
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<td>(0.18%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>(0.12%)</td>
</tr>
<tr>
<td>Abnormal behavior</td>
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<td>(0.12%)</td>
</tr>
<tr>
<td>Body height below normal</td>
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<td>(0.12%)</td>
</tr>
<tr>
<td>Condition aggravated</td>
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<tr>
<td>Drug ineffective</td>
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</tr>
<tr>
<td>Ear infection</td>
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</tr>
<tr>
<td>Expired drug administered</td>
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<td>(0.12%)</td>
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<tr>
<td>Failure thrive</td>
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<tr>
<td>Gastroenteritis</td>
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<td>Inappropriate schedule of drug administration</td>
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<td>Loss of consciousness</td>
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<tr>
<td>Regurgitation</td>
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<tr>
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<td>Rhinitis</td>
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<tr>
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</tr>
<tr>
<td>Accidental overdose</td>
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<tr>
<td>Altered state of consciousness</td>
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<tr>
<td>Analgesic therapy</td>
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</tr>
<tr>
<td>Asthenia</td>
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<td>(0.06%)</td>
</tr>
<tr>
<td>Preferred term</td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
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<td>Cold sweat</td>
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<tr>
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<tr>
<td>Contraindication to medical treatment</td>
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<tr>
<td>Decreased activity</td>
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<td>(0.06%)</td>
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<td>Eating disorders</td>
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<td>ECG repolarization abnormality</td>
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<td>Eye movement disorder</td>
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<tr>
<td>Fixed pupil</td>
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<tr>
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<tr>
<td>Frequent bowel movements</td>
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<tr>
<td>Hyperhydrosis</td>
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<tr>
<td>Hypersomnia</td>
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<td>Hypoacusis</td>
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<td>Hypophagia</td>
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<tr>
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<tr>
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<tr>
<td>Oedema peripheral</td>
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<td>Otitis media</td>
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<tr>
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<td>Peripheral vascular disorder</td>
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<td>Respiratory disorder</td>
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<tr>
<td>Respiratory syncytial virus bronchiolitis</td>
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<tr>
<td>Sinus arrest</td>
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<tr>
<td>Unspecified adverse event</td>
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<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>(0.06%)</td>
</tr>
<tr>
<td>Wrong technique in drug usage process</td>
<td>1</td>
<td>(0.06%)</td>
</tr>
</tbody>
</table>

AE: adverse effect.

* CUP data were reported by case; one patient could present ≥1 case. For the purpose of this review the worst case scenario has been taken, i.e. 1 case = 1 patient.
<table>
<thead>
<tr>
<th>Preferred term(s)</th>
<th>n</th>
<th>Propranolol (N = 3766) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE*</td>
<td>578</td>
<td>15.35%</td>
</tr>
<tr>
<td>Heart rate decreased</td>
<td>166</td>
<td>4.41%</td>
</tr>
<tr>
<td>Blood pressure decreased</td>
<td>156</td>
<td>4.14%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>118</td>
<td>3.13%</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>109</td>
<td>2.89%</td>
</tr>
<tr>
<td>Peripheral coldness</td>
<td>100</td>
<td>2.66%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>63</td>
<td>1.67%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>54</td>
<td>1.43%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>53</td>
<td>1.41%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>45</td>
<td>1.19%</td>
</tr>
<tr>
<td>Respiratory rate decreased</td>
<td>35</td>
<td>0.93%</td>
</tr>
<tr>
<td>Irritability</td>
<td>32</td>
<td>0.85%</td>
</tr>
<tr>
<td>Wheezing</td>
<td>29</td>
<td>0.77%</td>
</tr>
<tr>
<td>Nightmare</td>
<td>27</td>
<td>0.72%</td>
</tr>
<tr>
<td>Poor quality sleep</td>
<td>25</td>
<td>0.66%</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>24</td>
<td>0.64%</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>20</td>
<td>0.53%</td>
</tr>
<tr>
<td>URTI</td>
<td>19</td>
<td>0.50%</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>17</td>
<td>0.45%</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>16</td>
<td>0.42%</td>
</tr>
<tr>
<td>Hypokynesia</td>
<td>13</td>
<td>0.35%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0.32%</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>11</td>
<td>0.29%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>0.29%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>0.29%</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>10</td>
<td>0.27%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>9</td>
<td>0.24%</td>
</tr>
<tr>
<td>Viral infection</td>
<td>9</td>
<td>0.24%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>0.24%</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>8</td>
<td>0.21%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8</td>
<td>0.21%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0.21%</td>
</tr>
<tr>
<td>Hypotension diastolic</td>
<td>8</td>
<td>0.21%</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>8</td>
<td>0.21%</td>
</tr>
<tr>
<td>ECG PQ interval prolonged</td>
<td>7</td>
<td>0.19%</td>
</tr>
<tr>
<td>Agitation</td>
<td>6</td>
<td>0.16%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6</td>
<td>0.16%</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>0.16%</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>6</td>
<td>0.16%</td>
</tr>
<tr>
<td>Asthma</td>
<td>5</td>
<td>0.13%</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>5</td>
<td>0.13%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>0.13%</td>
</tr>
<tr>
<td>Blood pressure systolic decreased</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Overdose</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4</td>
<td>0.11%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Abnormal behaviour</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Abnormal weight gain</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Breath holding</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Preferred term(s)</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----</td>
<td>------</td>
</tr>
<tr>
<td><strong>Patients with at least 1 AE</strong></td>
<td>578</td>
<td>15.35%</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Feeding disorder</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Hypophagia</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Rash or dry skin</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Weight gain poor</td>
<td>3</td>
<td>0.08%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Dermatitis allergic</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Hypoglycaemic seizure</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Listless</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Obstructive airways disorder</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Pallor</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Poor feeding infant</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Seizure</td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Blood pressure diastolic decreased</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Body temperature decreased</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Dental caries</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Dyspnea exertional</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Hyporesponsive to stimuli</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Infantile spitting up</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Malaise</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Not coded</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Respiratory syncytial virus infection</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Seizure-like phenomena</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Streptococcal infection</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Stridor</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Tremor</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Vascular stenosis</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td>Xerosis</td>
<td>1</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

AE: adverse event/effect; ECG: electrocardiogram; URTI: upper respiratory tract infection.

*578 patients reported to have experienced at least one AE and 1399 patients reported to have experienced individual AEs by preferred term.