Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Propranolol hydrochloride

Proprietary Product Name: Hemangiol

Sponsor: Pierre Fabre Medicament Australia Pty Limited

August 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
ADR	Adverse drug reaction
AST	Aspartate aminotransferase
ATU	Temporary authorisation for use
AUC	Area under the plasma concentration time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time of intake until infinity
BP	Blood pressure
bpm	Beats per minute
CER	Clinical Evaluation Report
CHMP	Committee for Medicinal Products for Human Use (formerly the CPMP)
CI	Confidence interval
CL/F	Apparent oral clearance
Cmax	Maximum plasma concentration
CPMP	Committee for Proprietary Medicinal Products (now the CHMP)
CSR	Clinical Study Report
CV	Coefficient of variation
DPB	Diastolic blood pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Meaning
h	Hour/s
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IH	Infantile hemangioma
ITT	Intention to treat/Intent to treat
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond
PCSV	Potentially clinically significant value
PHACES	Posterior fossa brain anomalies, hemangiomas, arterial anomalies and cardiac defects and coarctation of the aorta syndrome
PI	Product Information
PK	Pharmacokinetic/s
PP	Per-protocol
PPK	Population pharmacokinetics
PR	Interval from start of the P-wave to start of the QRS complex
PT	Preferred Term (MedDRA)
QT	Interval from start of Q-wave to end of T-wave The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.
RBC	Red blood cell/s
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Meaning
SBP	Systolic blood pressure
SCS	Summary of clinical safety
TEAE	Treatment emergent adverse event
t½	Elimination half-life
US	United States
V0400 SB	Propranolol oral solution

I. Introduction to product submission

Submission details

Type of submission:	Major variation (extension of indications, new dose form and strength)
Initial Decision:	Rejected (19 June 2014)[1]
Final Decision:	Approved
Date of final decision:	18 June 2015
Active ingredient:	Propranolol hydrochloride
Product name:	Hemangiol
Sponsor's name and address:	Pierre Fabre Medicament Australia Pty Limited 1 Richardson Place, North Rye, NSW 2153
Dose form:	Oral solution
Strength:	3.75 mg/mL (as propranolol base, equivalent to 4.28 mg/mL of propranolol hydrochloride)
Container:	Bottle fitted with syringe
Pack size:	120 mL
Approved therapeutic use:	*Treatment of proliferating infantile haemangioma requiring systemic therapy:* • *Life-threatening haemangioma.* • *Ulcerated haemangioma with pain and/or lack of response to simple wound care measures.* • *Hemangiomas with a risk of permanent scars or disfigurement.*
Route of administration:	Oral
Dosage:	The recommended starting dose of Hemangiol is 0.15 mL/kg (0.5 mg/kg) (see Table 4 [in PI]) twice daily, taken at least 9 hours apart. After 1 week, increase the daily dose to 0.3 mL/kg (1.0 mg/kg) twice daily. After 2 weeks of treatment, increase the dose to 0.4 mL/kg (1.5 mg/kg) twice daily and maintain this for 6 months. Readjust the dose periodically as the child's weight increases.
ARTG number:	212274

[1] The initial Delegate's decision was reviewed in accordance with s.60(4) of the *Therapeutic Goods Act 1989*. For further details see the *Initial outcome* and *Final outcome* section of this AusPAR.

Product background

Propranolol is a non-selective beta adrenergic receptor blocker available in Australia since at least 1991 as propranolol hydrochloride 10 mg and 40 mg tablets for the treatment of angina pectoris, hypertension, prevention of migraine, cardiac dysrhythmias, certain intrinsic cardiac dysrhythmias, essential tremor, phaeochromocytoma (only with concurrent alpha-receptor blockade), hypertrophic subaortic stenosis, suspected or definite myocardial infarction, and Fallot's Tetralogy.

This AusPAR describes the application by Pierre Fabre Medicament Australia Pty Limited (the sponsor) to register a new dose form and strength for propranolol hydrochloride: an oral solution (trade name Hemangiol) containing propranolol hydrochloride 3.75 mg (propranolol base, equivalent to 4.28 mg/mL of propranolol hydrochloride), for the following new indication:

Treatment of proliferating infantile hemangioma requiring systemic therapy.

The oral solution dosage form is to facilitate the treatment of the target patient population (infants) as they cannot swallow tablets and to allow flexibility of dosing based on body weight of the patient.

Propranolol hydrochloride, sponsored by Pierre Fabre Medicament Australia P/L, was designated by the TGA as an orphan drug for *'the treatment of proliferating infantile hemangiomas requiring systemic therapy'* on 3 October 2012. The designated orphan indication and the proposed indication are identical.

Infantile hemangioma is a benign vascular tumour which may be present at birth in a small proportion of cases (termed congenital hemangioma) or evolve during the first 6 months of life. Non-congenital IHs enlarge during the first 6-12 months from the time the lesion evolves and thereafter regress spontaneously. Resolution may be complete without sequelae or with a variable degree of scarring or changes in skin pigmentation in a small proportion of incident cases. Once spontaneous regression has occurred, the lesion does not recur. Prior to complete resolution, complications of IH are determined by their anatomical position and may include: airway obstruction, superficial ulceration, haemorrhage, disturbance of function, platelet consumption coagulopathy, high-output heart failure (in the presence of multiple and/or large lesions) and acquired hypothyroidism in patients with liver hemangioma[2].

The exact pathogenesis of IH is not established and does not have a recognised pattern of inheritance. Propranolol was serendipitously found to have a suppressive effect on growth during the proliferative phase of growth. Propranolol has been shown to suppress angiogenesis in vitro and it is reported that the growth of IH stem cells, as compared to other endothelial cells, is inhibited by propranolol[3]. These findings may explain the observations from non-randomised clinical trials that propranolol use may be useful in treating IH. However, IH stem cells do not undergo apoptosis following propranolol exposure, the clinical correlate of which is that patients treated with propranolol may be unresponsive to, or relapse following the cessation of, treatment[4].

In Australia, the incidence of IH has been estimated as 2.6% of the overall birth cohort (309,582 total births in 2013); a greater incidence in infants delivered prematurely is seen.

There are currently no registered products for the treatment of IH however given the vast majority of medicines used in the paediatric population are used 'off-label', this does not, and

[2] Konrad D et al. Spontaneous regression of severe acquired infantile hypothyroidism associated with multiple liver hemangiomas. *Pediatrics* 2003:Dec; 112:1424-1426.
[3] Lamy, S., Lachambre, M.P., Lord-Dufour, S., Béliveau, R. Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells. *Vascul. Pharmacol*. 2010:53;200-208.
[4] Kum, J. Khan, Z. Propranolol inhibits growth of hemangioma-initiating cells but does not induce apoptosis. *Pediatric Research* 2014:75;381-388.

has not, precluded their use. Indeed contemporary methods to treat IH in Australia, in routine clinical practice and clinical trial settings, include the medications: corticosteroids, beta-blockers (including propranolol and timolol), interferon alpha and vincristine, or physical treatment using either pulsed dye laser or cryotherapy[5, 6, 7].

Regulatory status

At the time the TGA considered this application a similar application had been approved in the USA and European Union (EU) and was under consideration in Switzerland and Canada.

Using the same dossier, the EMA and FDA have approved Hemangiol for different indications:

The US indication is 'treatment of proliferating infantile hemangioma (IH) requiring systemic therapy'

The European indication is:

'Treatment of proliferating IH requiring systemic therapy:

Life-threatening hemangioma

Ulcerated hemangioma with pain and/or lack of response to simple wound care measures

Hemangiomas with a risk of permanent scars or disfigurement

It is to be initiated in infants aged 5 weeks to 5 months'

Product Information

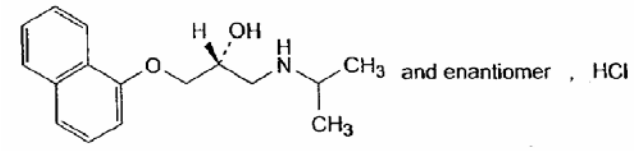
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI please refer to the TGA website at <https://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Introduction

The structure of propranolol hydrochloride is shown in Figure 1:

Figure 1: Structure of propranolol hydrochloride



[5] Goelz, R. et al. Prospective controlled study to evaluate cryocontact therapy for infantile haemangioma in preterm infants. *Archives of Disease in Childhood Fetal & Neonatal* 2014; 0:F1. doi:10.1136/archdischild-2013-304577.
[6] Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. *Arch Dermatol* 2010:146;564–565.
[7] Chan, H. McKay, C. Adams, S. Wargon, O. RCT of timolol maleate gel for superficial infantile hemangioms in 5- to 24- week olds. *Pediatrics* 2013: 131;e1739.

Drug substance (active ingredient)

Propranolol hydrochloride is Biopharmaceutics Classification System (BCS) Class 1, that is, it has high solubility and high permeability and the formulation is not expected to affect bioavailability. Propranolol is basic and is formulated as the hydrochloride.

Propranolol hydrochloride contains one chiral centre. The drug substance used in the manufacture of the oral solution is the racemate, as is that used in the tablets. For the currently registered tablets and indications, the (S)-(–)-enantiomer is the active form.

There exist pharmacopoeial monographs (British, European and United States Pharmacopoeias) for the drug substance propranolol hydrochloride. Control of the drug substance is acceptable.

Drug product

The drug product proposed for registration is a colourless to slightly yellow, clear, oral solution with a fruity odour. It contains 3.75 mg/mL propranolol, which is equivalent to 4.28 mg/mL of propranolol hydrochloride. The proposed pack size is 120 mL.

The oral solution dosage form was developed in order to avoid use of the tablets for infants. The currently registered tablets are labelled in terms of propranolol hydrochloride content whereas the proposed oral solution is labelled in terms of propranolol content; this is potentially confusing and may result in dosing variability if patients are switched between formulations (for example, a 10 mg propranolol hydrochloride tablet contains 8.7 mg propranolol; note that the oral solution bottle contains 120 mL, corresponding to 450 mg propranolol). The proposed PI includes an appropriate statement on the difference in labelled content for the different dosage forms.

Hemangiol oral solution contains, amongst other excipients, propylene glycol as the major component of two flavourings. Generally, there is potential concern of propylene glycol exposure in neonates. A statement on quantitative exposure to propylene glycol has been included in the PI. Based on toxicological advice, there are no concerns with the individual ingredients of the two flavours.

The oral solution is packaged in a glass bottle and is supplied with an oral syringe for dose delivery. The bottle is amber glass type III with a polyethylene insert (designed to connect with the oral syringe). The oral syringe is a polypropylene barrel and polyethylene plunger, graduated in mL from 0.3 mL to 5 mL in 0.1 mL increments. Proposed doses range from 0.3 mL to 4.8 mL. Based on clinical advice, use of the one syringe to cover the wide range of possible doses is acceptable.

The sponsor had committed to provide the report of a study into the child-resistance of the cap in simulated conditions of use (as per Therapeutic Goods Order No. 80, *Child-Resistant Packaging Requirements for Medicines*).

Adequate stability data have been provided to support the proposed shelf-life of 30 months for storage below 30 °C with a condition of 'Do not freeze'. The oral solution may be administered neat or by diluting in milk or fruit-juice. Compatibility studies are described and in-use stability data support use of the diluted product within 2 h of dilution.

The oral solution does not contain a preservative; it is self-preserving. All microbiological issues have been resolved.

Biopharmaceutics

A bioequivalence study (propranolol hydrochloride tablets (as supplied to the European market) versus propranolol hydrochloride oral solution (developmental formulation) in

adults) was provided and showed similar pharmacokinetic (PK) profiles for the two dosage forms (tablet versus oral solution); the study was not reviewed given that propranolol hydrochloride is BCS Class 1 and therefore the different dosage forms are expected to be bioequivalent (solid oral products are effectively oral solutions in use) and switching between formulations is not relevant.

Advisory committee considerations

This application was not submitted for advice from the Pharmaceutical Chemistry Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

Registration is recommended with respect to chemistry, manufacturing, and controls of the proposed product, subject to provision of acceptable data on the child-resistance of the container closure.

III. Nonclinical findings

Introduction

The nonclinical part of the submission is largely literature-based, with 98 references cited in the sponsor's nonclinical overview, which included an overview of nonclinical testing strategy, pharmacology, PK, and toxicology of propranolol. The key nonclinical study provided in this submission is a good laboratory practice (GLP) compliant repeat dose toxicity study in juvenile rats. Ten juvenile animal literature references relevant to the safety assessment of propranolol in children are also summarised.

Pharmacology

Primary pharmacodynamics

Propranolol is a non-selective β-adrenergic receptor blocker and a well-known therapeutic substance for the treatment of a variety of conditions. The proposed treatment of hemangioma in children is a new indication. No studies have been performed with propranolol in animal models of hemangioma. The following are postulated by the sponsor as possible mechanisms of action for the treatment of hemangiomas and discussed in the sponsor's nonclinical overview and pharmacology written summary:

- Vasoconstriction, reducing blood flow in highly vascularised hemangioma tissues;
- Inhibition of angiogenesis by blocking the catecholamines-stimulated vascular endothelial growth factor (VEGF) expression and endothelial cell proliferation via β2-adrenoceptors (although propranolol was found not to suppress VEGF-A production in hemangioma-derived stem cells and endothelial cells (unpublished data cited by Greenberger and Bischoff[8]) and by inhibiting matrix metalloproteinase (MMP)-9, which are critical for angiogenesis; and
- Induction of apoptosis of capillary endothelial cells.

[8] Greenberger S, Bischoff J Infantile hemangioma – mechanism(s) of drug action on a vascular tumor. *Cold Spring Harb Perspect Med*. 2011:1: a006460.

The proposed mechanisms are plausible.

Secondary and safety pharmacology

Since propranolol is a well-known drug substance and has been used in adults for many decades, the secondary pharmacological activities are not discussed in this evaluation. The potential effects on central nervous functions in infants were investigated in the juvenile repeat dose toxicity study in rats (see *Toxicicology* below). Cardiovascular and respiratory functions were not specifically investigated in the juvenile rat study, but effects of β-blockers on cardiovascular and respiratory functions in humans are well known and are addressable by clinical data.

Two published studies in young rats by intraperitoneal (IP) or subcutaneous (SC) administration of 5 or 15 mg/kg/day propranolol showed changes in brain amines and altered behaviour[9, 10] but no effects on motor activity, learning and memory and other neurobehavioral activities were seen in the well-conducted juvenile rat study (see below).

Toxicology

An 18 day repeat dose toxicity study was carried out in juvenile rats to investigate the potential effect of propranolol on development following daily oral administration from postnatal day (PND) 4 to PND 21 at dose levels of 10, 20 and 40 mg/kg body weight/day. Systemic exposures in juvenile rats decreased with increasing age despite repeated dosing. The exposures at the high dose were higher than the exposures in paediatric patients but the exposures at the low dose and mid dose were lower than or similar to the clinical exposures (see Table 1 below).

Table 1: Animal/human exposure comparison

	Dose (mg/kg/day)	Cmax (ng/mL)	$AUC_{0\text{-}24\ h}$ (ng.h/mL)	Animal/human exposure ratio (Cmax)*	Animal/human exposure ratio ($AUC_{0\text{-}24\ h}$)*
PND 4 - male (First dose)	10, 20, 40	196, 229, 466	537, 843, 3387	2.4, 3, 6	0.6, 1, 4
PND 4 - female (First dose)	10, 20, 40	161, 568, 948	456, 1178, 3030	2.0, 7, 12	0.5, 1.4, 3.5
PND 21 - male (Last dose)	10, 20, 40	17.6, 43.1, 325	54, 262, 2516	0.22, 0.5, 4	0.06, 0.3, 3
PND 21 - female (Last dose)	10, 20, 40	59.3, 88.2, 229	237, 221, 1051	0.8, 1.1, 3	0.28, 0.26, 1.2
*human Cmax 79.2 ng/mL and $AUC_{0\text{-}24\ h}$ 860 ng.h/mL ($AUC_{0\text{-}12\ h}$ 430 ng.h/mL x 2) at 3 mg/kg/day in two divided doses for 10 weeks (from Study # V00400SB102)					

Cmax = maximum concentration; $AUC_{0\text{-}24\ h}$ = area under the concentration-time curve over time zero to 24 h

Two high dose pups were either sacrificed or found dead after 4 doses on PND 7, and the deaths were considered to be possibly treatment related.

The most notable observation in the juvenile toxicity study was a decrease in body weight gain in both sexes at 40 mg/kg/day (by 13% in males and 9% in females cf. the control group), which was reversible after cessation of treatment. The effect on body weight gain was consistent with findings in published juvenile rat studies. An interesting finding of the juvenile rat study was significantly higher body weights on PND 88 (approximately 10 weeks

[9] Erdtsieck-Ernste B.h.W. et al. Chronic propranolol treatment in developing rats: acute and lasting effects on monoamines and beta-adrenergic receptors in the rat brain. *Brain Res. Bull*. 1991:26:731-737.
[10] Hilakavilla L.A. et al. Early treatment with propranolol affects development of brain amines and behaviour. *Psychopharmacol*. 1988:96:353-359.

after cessation of dosing) in the low dose group than in other groups (by about 8% in both sexes compared with the control and mid- and high dose groups).

Decreased extramedullary haematopoiesis in spleen and liver were observed in the high dose animals, associated with lower spleen and liver weights. No microscopic examination was conducted for the low and mid dose groups, but decreased spleen weights in the low and mid dose female groups suggest the same histological changes (that is, decreased extramedullary haematopoiesis) may be also present in females at lower doses.

Full blood counts showed no abnormalities in red blood cell (RBC) parameters; however, low platelet counts, which were evaluated in only two rats (one per sex), were noted at 40 mg/kg/day (below the laboratory reference range and the concurrent control group values). It is uncertain whether the low platelet counts were incidental findings or due to propranolol treatment, but an effect of propranolol treatment cannot be excluded. No abnormalities were observed in bone marrow (sternum). The mechanisms for these findings are unclear. It is possible that propranolol may cause thrombocytopenia in paediatric patients.

A small increase in plasma creatinine was observed in males at 40 mg/kg/day. Urine volume was decreased in females at 20 mg/kg/day and both sexes at 40 mg/kg/day, without changes in urinary specific gravity (urinary electrolytes were not analysed). There were no renal lesions by histological examination. Food and water consumption during the dosing period were not measured in the study. It is unknown whether the reduced urine volume was secondary to lower water intake. It is possible that reduced urine output reflect reduced renal blood flow by propranolol as observed in adult rats[11]. Propranolol treatment of infants may reduce urinary output.

Plasma triglycerides levels were increased in males at 20 mg/kg/day (by 75%) and in both sexes at 40 mg/kg/day (by 146% in males and 50% in females). The increased plasma triglycerides may indicate impaired hepatic function, but there was no other evidence of hepatic effects (biochemistry and histology) except for decreased extramedullary haematopoiesis discussed above.

All the above effects were reversible after cessation of dosing.

Treatment of juvenile rats did not affect long bone growth, development, functional/motor activity, learning/memory, cardiac biomarkers (atrial natriuretic peptide, B-type natriuretic peptide, and troponin-I), and reproduction (oestrous cycle, seminology, mating/fertility and gestation). Cardiovascular functions and blood pressure (BP) were not monitored in the study, but they can be addressed by clinical data.

There are no other nonclinical toxicity studies. This is acceptable given the long clinical use history of propranolol.

Genotoxicity

The sponsor provided an overview of published genotoxicity studies on propranolol. The following assessment is based on the review on β-adrenergic blockers by Jackson and Fishbein (1986)[12] and studies published after the Jackson and Fishbein review.

There was no evidence of mutagenicity in bacteria (Ames) tests[5,13,14], although the FDA-approved labelling for the propranolol product (InnoPran XL Extended Release Capsules)

[11] Brenner BM et al. Comparative effects of propranolol and nadolol on renal blood flow in normal rats and rats with congestive heart failure. *Am Heart J.* 1984:108:1144-1147.
[12] Jackson CD, Fishbein L A toxicological review of beta-adrenergic blockers. *Fund Appl Toxicol* 1986:6:395-422.
[13] Zhang S et al. Derivatives of β-adrenergic antagonists. N-nitrosopropranolol and N-hydroxypropranolol and its aldonitrone. *J Med Chem* 1983:26: 455-458.

states equivocal evidence of mutagenicity in bacteria (*Salmonella typhimurium* strain TA1538) based on differing results from Ames tests performed by different laboratories[15].

Propranolol did not cause deoxyribonucleic acid (DNA) damage to rat and human hepatocytes or Chinese hamster V79 cells in vitro at the highest noncytotoxic concentration (up to 3 mM)[16] or in human fibroblasts at up to 65 ug/mL. In an in vitro assay with rat hepatocyte nuclei, propranolol produced dose dependent DNA fragmentation. Analysis of the DNA in neutral gradients indicated that the damage was single-strand breaks (not double-strand breaks). When administered in vivo, propranolol produced no detectable hepatic DNA damage in rats.

In an in vivo micronucleus assay, propranolol at > 74.5 mg/kg IP (2 doses with a 24 h dosing interval) induced a significant increase of micronucleated polychromatic erythrocytes in mice. No effect was observed at 37.25 mg/kg[17]. In the same article, it was reported that propranolol did not induce chromosomal aberrations in spermatocytes in mice at up to 111.75 mg/kg/day IP for 5 days.

The weight of evidence from in vitro and in vivo studies indicates that propranolol is unlikely to present a genotoxic risk to patients.

Carcinogenicity

One published article reported carcinogenicity studies of propranolol in mice and rats[18]. In the studies, propranolol was used as a reference agent for sotalol. Only one dose level of propranolol was tested. Propranolol was given to Swiss CD-l mice (60 per sex) at 100 mg/kg/day in the diet for 78 weeks. Following the treatment period, the mice were then observed without treatment for an additional 13 weeks before necropsy. A similar study was performed in Long-Evans rats (60 per sex) with a propranolol dose of 37.5 mg/kg/day in the diet for 79 weeks with an additional treatment free period until the end of 2 years (from the start of dosing). Neoplastic lesions in propranolol-treated groups were comparable to the concurrent control group in both species.

FDA approved labelling for the propranolol product (InnoPran XL Extended Release Capsules) states that 'In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis.' These carcinogenicity studies have not been reviewed by the TGA.

Nonclinical summary and conclusions

- The nonclinical component of the dossier consists of literature reviews of pharmacology studies relevant to the proposed indication and toxicity studies in juvenile animals, and one well conducted juvenile rat study including toxicokinetics.
- The efficacy was not studied in animal models of hemangioma. The proposed mechanisms of action for the treatment of hemangioma are plausible:
  - Vasoconstriction, reducing blood flow in highly vascularised hemangioma tissues;

[14] Hussain SS et al. DNA strand breaks and mutations caused by penbutolol, a beta-blocker. *Mut Res* 1988:204: 675-682.
[15] Physician's Desk Reference (2013 online): InnoPran XL (propranolol hydrochloride) Extended Release Capsules. PDR Network.
[16] Robbiano L et al. Formation of the N-nitroso derivatives of six β-adrenergic-blocking agents and their genotoxic effects in rat and human hepatocytes. *Cancer Res* 1991:51:2273-2279.
[17] Aruna N, Krishnamurthy N Mutagenic evaluation of propranolol in somatic and germ cells of mice. *Mut Res* 1986:173:207-210.
[18] Weikel JH Jr, Kelly WA Tumorigenicity assays of sotalol hydrochloride in rats and mice. *J Clin Pharmacol* 1979:19:591-604.

  - Inhibition of angiogenesis by blocking the catecholamines-stimulated VEGF expression and endothelial cell proliferation via β2-adrenoceptors and by inhibiting matrix metalloproteinase (MMP)-9, which are critical for angiogenesis; and
  - Induction of apoptosis of capillary endothelial cells.
- The findings in the repeat dose study in juvenile rats were similar to those previously described for propranolol, mainly decreased mean weight body gain. Other findings were decreased extramedullary haematopoiesis in spleen and liver (associated with lower spleen and liver weights), decreased platelet counts, decreased urine volume, and increased plasma triglycerides levels. All the effects were reversible.
- Treatment of juvenile rats did not affect long bone growth, development, functional/motor activity, learning/memory, cardiac biomarkers (atrial natriuretic peptide, B-type natriuretic peptide, and troponin-I), and reproduction (oestrous cycle, seminology, mating/fertility and gestation). Cardiovascular functions and BP were not monitored in the study, but effects of β-blockers on cardiovascular and respiratory functions in humans are well known and are addressable by clinical data.
- The weight of evidence from in vitro and in vivo studies indicates that propranolol is unlikely to present a genotoxic risk to patients.
- Long-term carcinogenicity studies conducted via dietary administration in mice and rats showed no evidence of tumourigenicity.

Conclusions and Recommendation

- In the juvenile rat study, propranolol treatment resulted in decreases in blood platelet counts and urinary output and increases in plasma triglycerides level at exposures lower or slightly higher than the clinical exposure. The effects were reversible after cessation of treatment. These effects may occur in children with the proposed treatment regimen.
- There are no nonclinical objections to the registration of Hemangiol as proposed[19].

Recommended revisions to nonclinical statements in the proposed PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This is an application to register a new dosage form, a new strength and a new indication for propranolol hydrochloride: Hemangiol (propranolol hydrochloride) 3.75 mg/mL oral solution. The proposed indication is:

> *Treatment of proliferating infantile hemangioma requiring systemic therapy.*

Clinical Rationale

Infantile hemangiomas (IHs) are common neoplasms composed of proliferating endothelial-like cells. Infantile hemangiomas are the most common vascular tumours of childhood and

[19] The safety of the formulation excipients was assessed in a separate nonclinical evaluation not shown here.

have been estimated to occur in 3% to 10% infants (Frieden et al., 1997[20]; Haggstrom et al., 2007[21]; Hoornweg et al., 2005[22]; Kilcline and Freiden, 2008[23]). In a recent prospective Australian study, the incidence of superficial and mixed IHs over the first 6 weeks of life was found to be 2.6% (28/1065 babies) (Dickson et al., 2011[24]).

Infantile hemangiomas are benign tumours that are not usually present at birth, but appear within the first few weeks of life (Chen et al., 2013[25]). In most cases proliferation continues for 3 to 6 months, although in rare cases it can continue for up to 12 months (Paediatrics Manual, Westmead, 2009[26]). In a prospective cohort study of 526 IHs in 433 patients, most IH growth occurred before the age of 5 months (Chang et al., 2008[27]). Spontaneous involution begins after the maximum size is reached, usually between 9 and 12 months of age, and is complete in 50% of children by the age of five and in 90% of children by the age of nine (Bruckner and Frieden, 2003[28]; Paediatrics Manual, Westmead, 2009). Known risk factors for the development of IH are: female sex (female to male ratio of 2.4:1), Caucasian ethnicity, low birth weight (especially < 1500 g), and infants of mother's with multiple gestations (Haggstrom et al, 2007; Sundine and Wirth, 2007[29]; Drolet et al., 2008[30]).

Treatment for IHs usually involves active observation only, as most follow an uncomplicated clinical course and 80-90% regress spontaneously (Storch and Hoeger, 2010[31]). In a publication by Bower's et al. (1960[32]), '*140 children with 169 naevi [from a UK clinic] were watched until cured, or...for a minimum of 5 years*' and approximately 50% of the naevi resolved by the age of 5 years and 70% by the age of 7 years. Furthermore, only about 6% of the naevi constituted '*any cosmetic handicap'. Bowers et al. (1960) also noted that there was 'almost exact agreement [between 49% of hemangiomas resolving with very good results by age of 5 and] and Lister's (Lister, 1938[33]) figure of 53% excellent results at the age of 5*'.

Although most IHs are innocuous, some are associated with complications that can be life-threatening (Storch and Hoeger. 2010). In a prospective cohort study of a consecutive sample of 1058 children aged ≤ 12 years with IHs from 7 US paediatric dermatology clinics enrolled between September 2002 and October 2003, approximately 24% experienced complications related to their IHs (Haggstrom et al., 2006[34]). The most commonly occurring complication was reported to be ulceration (16.0%), followed by threat to vision (5.6%), airway obstruction (1.4%), auditory canal obstruction (0.6%), and cardiac compromise (0.4%) (Haggstrom et al., 2007). It was observed that large size, facial location, and/or segmental morphology were the most important predictors of short-term outcomes as measured by

[20] Frieden IJ et al. Guidelines of care for hemangiomas of infancy. *J Am Acad Dermatol*. 1997:Oct;37(4):631-7.
[21] Haggstrom et al. Prospective study of infantile hemangiomas: demographic, prenatal and perinatal characteristics. *J Pediatr* 2007:150:291-294.
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[25] Chen et al. Infantile hemangiomas: an update on pathogenesis and therapy. *Pediatrics* 2013; 131(1):99-108.
[26] Paediatrics Manual. The Children's Hospital at Westmead Handbook (2nd Edition), 2009; Eds Kilham H, Alexander S, Wood N, Isaacs D.
[27] Chang LC et al. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics* 2008: Aug;122(2):360-367.
[28] Bruckner AL, Frieden IJ. Hemangiomas in Infancy. *J Am Acad Dermatol*. 2003:138;156-157.
[29] Sundine MJ and Wirth GA. Hemangiomas: an overview. *Clinical Pediatrics*. 2007: Apr;46(3);206-221.
[30] Drolet BA et al. Infantile hemangiomas: an emerging health issue linked t an increased rate of low birth weight infants. *J Pediatr* 2008:153;7125-5.
[31] Storch CH and Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*. 2010:Aug;163(2);269-274.
[32] Bowers RE et al. The natural history of the strawberry nevus. *Arch Dermatology*. 1960:82;59-72.
[33] Lister W. Natural history of Strawberry Naevi. *Lancet* 1938:1;1429.
[34] Haggstrom AN et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics*. 2006:Mar;117(3);698-703.

complication and treatment rates for IHs. In addition, although most IHs are not worrisome, it has been estimated that approximately 12% are significantly complex requiring referral to specialists for consideration of treatment (Drolet et al., 2013[35]). The sponsor provided a tabulated summary of the complications of IHs derived from a number of studies.

The sponsor's clinical overview states that IHs '*are extremely heterogeneous in terms of size, location, risk of complication, rate of proliferation and involution, and results after involution. For this reason, there is no established severity classification and the decision to treat by systemic therapy is individualised, weighing therapeutic risks against potential benefits. As soon as poor prognosis factors are present, a decision regarding treatment should be made without further delay, during the proliferative phase of the disease*'.

The clinical overview refers to Guidelines for the care of infants with HIs outlining the indications for treatment developed before the use of propranolol for treatment of the condition (Frieden et al., 1997[36]). These general indications for treatment are:

- Life and function threatening IHs (such as those causing impairment of vision, respiratory compromise caused by airway lesions, congestive heart failure, hepatic involvement).
- IHs in certain anatomical locations that often leave permanent scars or deformity, especially the nose, lip, ear, and glabellar area.
- Large facial IHs, especially those with a prominent dermal component (more likely to leave permanent scarring).
- Smaller hemangiomas in exposed areas, such as the face and hands, may be considered for treatment with modalities unlikely to cause scarring or significant side effects.
- Ulceration.
- Pedunculated hemangiomas (likely to leave significant fibrofatty tissue after involution).

The sponsor's clinical overview states that the target indication for the use of propranolol for the treatment of IHs includes the general criteria noted above (Frieden et al., 1997), as well as an enlargement of the criteria to include IH with a potential risk of disfigurement (not restricted to facial or exposed areas).

In order to avoid scarring, disfigurement, or interference with function a significant proportion of patients with IH will require systemic treatment (Haggstrom et al., 2007; Chen et al., 2013). In addition to systemic treatments, non-systemic therapies such as surgery and laser treatments have been used to treat IHs. There are currently no medicines approved in Australia for the treatment of IHs, and all medicines used to treat the condition are being used 'off-label'. The sponsor states that corticosteroids for the treatment of severe forms of angiomas in infants are registered in only two countries (France, Germany), and there are currently no other products approved in any country for the treatment of IHs. Prior to 2008, corticosteroids (systemic, topical, or intralesional) were used for first-line therapy of IHs (Dickson et al., 2011; Chen et al., 2013), while other systemic therapies included interferon and vincristine (Chen et al., 2013).

Treatment of IHs with propranolol was first reported in 2008 (Léauté-Labrèze et al., 2008[37]), and since then there have been a number of further reports suggesting that propranolol is an effective treatment for IHs. Propranolol for the treatment of IHs has been reported to be replacing corticosteroids for first line therapy of IHs (Dickson et al., 2011; Chen et al., 2013). The use of propranolol for the treatment of IHs has recently been the subject of a USA

[35] Drolet BA et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 2013:Jan;131(1);128-140.
[36] Frieden IJ et al. Guidelines of care for hemangiomas of infancy. *J Am Acad Dermatol*. 1997:Oct;37(4);631-7.
[37] Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *NEJM* 2008:Jun 12;358(24):2649-51.

Consensus Conference sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and funded by the National Institute of Health (Drolet et al., 2013).

Three possible mechanisms of action of propranolol for the treatment of IH have been postulated: vasoconstriction, which is a classical consequence of beta-adrenergic blockade and might result in decreased perfusion of the IH lesion perfusion; inhibition of angiogenesis characterised by decreased proliferation of vascular endothelial cells, reduction in neovascularisation and formation of vascular tubules, and reduction of the secretion of Matrix Metalloproteinase 9 which is crucial for endothelial cell migration; and apoptosis via beta2-adrenoreceptor mediated blockade of capillary endothelial cell proliferation (Storch and Hoeger, 2010; sponsor's *Summary of clinical pharmacology studies*).

Evaluator comment: The sponsor provided a comprehensive an acceptable clinical rationale for propranolol for the treatment of proliferating IH requiring systemic therapy. The sponsor considers that there is an unmet need for treatment of IHs and seeks to register a propranolol formulation specifically designed for infants to meet this need. However, it is noted that there is a high spontaneous resolution rate for IHs and that, although some lesion can be life threatening, the pivotal efficacy and safety study specifically excluded patients with life threatening IHs and other high-risk lesions.

Guidance

There are no TGA approved guidance documents specifically relating to the treatment of IHs.

Contents of the clinical dossier

The clinical data comprised the following:

- 1 Phase I comparative bioavailability (BA) and bioequivalence (BE) study in healthy adult males;
- 1 Phase I PK and initial tolerability study in infants with IH, including a population pharmacokinetic (PPK) report;
- 1 pivotal Phase II/III efficacy and safety study in infants with IH;
- 1 protocol from an ongoing uncontrolled, extension study in infants with IH; Integrated Safety Study (ISS) tables and Statistical Analysis Plan (SAP); 4 Temporary Authorisation for Use (ATU) reports identified as 'reports of post-marketing experience', but actually reports of patients treated in France under a Compassionate Use Program (CUP); literature references.
- *Summary of clinical pharmacology studies*; *Summary of clinical efficacy*; *Summary of clinical safety* (SCS); literature references; synopses of individual studies.

Paediatric data

The pivotal Phase II/III clinical and efficacy study (201) was undertaken in infants with proliferating IH aged from 30 to 150 days. The proposed indication for Hemangiol is applicable only to infants in this age group with proliferating IH requiring systemic therapy.

Good clinical practice

The studies forming the sponsor's clinical development program for the proposed product for the proposed indication were undertaken in compliance with the principles of good clinical practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included two studies providing PK data (Study V004 SB 101 2A; Study V00400 SB 1 02); these two studies are referred to as Study 1012A and Study 102, respectively, in this section on *Clinical findings*. In addition to a non-compartmental PK analysis in infants with IH, Study 102 also included a population pharmacokinetic (PPK) analysis in this patient group identified as V0400 101 and referred to as the PPK report. The two studies (including the PPK report) have been evaluated and relevant data from these studies (including the PPK report) have been included in the evaluation. Studies 1012A, 102 and the PPK report are briefly outlined below (Table 2).

Table 2. Brief outline of the studies providing pharmacokinetic data.

Study	PK topic	Population (n)	Primary objective	Treatments
1012A, Phase I, single-centre (France), single-dose, randomised, open-label, 2-period, crossover, washout ≥ 3 days.	BA/BE/PK of oral solution and tablet formulations in healthy male adults.	Healthy male subjects; aged 20 to 41 years (12 m)	Evaluation of single dose PK parameters of new propranolol oral solution compared with oral tablet	Propranolol HCL oral solution (5 mg/mL), 80 mg dose. Avlocardyl 40 mg tablets (propranolol HCl), dose 2 x tabs = 71.18 mg.
102, Phase I, open-label, single-country (France), multi-centre (4), repeated dose (twice daily (BID)), 12 weeks duration.	Steady-state PK of propranolol and 4-OH-propranol (metabolite) in infants with IH.	Infants with IH; Group 1 aged 35 to 90 days (inclusive); Group 2 aged 91 to 150 days (inclusive). (6 m, 16 f)	Characterise steady-state PK of propranolol in infants with IH; PK assessment at Day 28 after 4 weeks treatment in Group 1 and at Day 84 after 12 weeks treatment in Group 2.	Propranolol oral solution (3.75 mg/mL) administered at a dose of 1 mg/kg/day from Day 0, 2 mg/kg/day from Day 7, and 3 mg/kg/day from Day 7 to 84. Dose given BID (morning and late afternoon).
PPK report based on data from Study 102.	PPK	166 non-zero drug observations and 109 non-zero 4-OH metabolite observations. (10/Group 1, 12/Group 2)	To describe PK of propranolol and to describe the inter-subject variability in the PK of the drug.	PK of propranolol and 4-OH metabolite based on 22 patients sampled twice in the titration period (1-2 mg/kg/day) and six times in the fixed-dose period (3 mg/kg/day).

BA: Bioavailability; BE: Bioequivalence; BID: twice daily; m: males; f: females.

Evaluator's conclusions on pharmacokinetics

The submission included two studies with PK data relating to the oral solution of propranolol (Study 102A in healthy adults and Study 102 in infants with IH). In addition, the submission included a PPK analysis on data from infants with IH from Study 102.

There was no study in either healthy adults or infants with IH comparing the proposed propranolol oral solution (3.75 mg/mL) with an Australian marketed propranolol tablet. The sponsor provided a justification for not submitting a relative bioavailability study comparing the oral solution with an Australian marketed product, but the justification included in vitro dissolution data comparing the French sourced propranolol tablet with a US marketed tablet. The absence of a relative bioavailability study comparing the propranolol oral solution (3.75 mg/mL) proposed for registration with an Australian marketed propranolol tablet is considered to be a deficiency in the submission. However, this deficiency is offset to some extent by the presence of a study in infants with HI that adequately characterises the PK of propranolol in the proposed target population. There was no absolute bioavailability study comparing the proposed propranolol oral solution with an intravenous (IV) formulation of propranolol. However, the absence of such a study should not preclude approval of the solution, as it is well known that propranolol is almost completely absorbed following oral administration and undergoes significant first-pass hepatic metabolism.

In Study 1012A, the relative bioavailability of a propranolol oral solution (5 mg/mL) and a propranolol tablet (40 mg) marketed in France was compared in 12 healthy adult males aged between 18 and 45 years in a cross-over trial. The sponsor considered this to be a supportive study in adults undertaken to evaluate the PK of propranolol oral solution before it was administered to infants. In this study, the bioavailability of the oral solution was greater than the oral tablet assessed by both the maximum concentration (Cmax) (22% greater) and the area under the concentration-time curve over time zero to infinity ($AUC_{0-\infty}$; 20% greater) following administration of single doses of the two formulations dose normalised to 80 mg. The plasma concentration-time profiles for the two formulations (dose normalised to 80 mg) were comparable when measured over a 24 h period following single dose administration. The median time to reach maximum concentration (Tmax) values were similar for the oral solution 80 mg and the oral tablet 70.18 mg (1.33 h [range (h): 1, 2] and 1.67 h [range (h): 0.67, 3), respectively), indicating rapid absorption following administration. The mean half-life (t½) values were similar for the oral solution 80 mg and the oral tablet 70.18 mg (4.41 and 4.19 h, respectively), suggesting that both formulations are likely to be completely eliminated approximately 21 h after dosing. Inter-subject variability in Cmax and $AUC_{0-\infty}$ values was moderate following single dose administration of the oral solution (coefficient of variation (CV) = 27% and 39%, respectively), while inter-subject variability in Cmax and $AUC_{0-\infty}$ values was marked following single dose administration of the tablet formulation (CV = 95% and 92%, respectively).

In Study 102, the steady-state PK of propranolol and the 4-OH-propranol metabolite following administration of the 3.75 mg/kg solution twice daily (BID) were characterised using non-compartmental analysis in 23 infants with IH, stratified by age into two groups (Group 1 [n=10] aged 35 to 90 days, Group 2 [n=13] aged 91 to 150 days). All patients received 1 mg/kg/day from Day 0, 2 mg/kg/day from Day 7, and 3 mg/kg/day from Day 14 to Day 84. The assessment of steady-state PK took place at Day 28 (that is, after 4 weeks treatment) in Group 1 and at Day 84 (that is, after 12 weeks treatment) in Group 2.

In Study 102, during the titration period (repeated BID oral administration of propranolol at 1 and 2 mg/kg/day) and at the target dose (3 mg/kg/day), concentrations of propranolol quantified before the morning administration (minimum plasma concentration, Cmin) increased with dose. In Group 1, median Cmin increased from 4.69 ng/mL at Day 7 to 22.4 ng/mL at Day 28, and in Group 2, median Cmin increased from 3.74 ng/mL at Day 7 to 10.1 ng/mL at Day 84. For 4-OH propranolol, most Cmin levels were below the limit of quantification (0.5 ng/mL) during the titration period, and at steady-state at weeks 4 (Group 1) and 12 (Group 2).

In Study 102, geometric mean propranolol steady-state Cmax levels were similar in the two age groups (78.5 and 79.2 ng/mL in Groups 1 and 2, respectively), while median Tmax values were 2 h in both groups. The geometric mean propranolol $AUC_{0-9\,h}$ was higher in the younger

age group than in the older age group (455 and 373 ng.h/mL, respectively), while the weight adjusted geometric mean total clearance (CL) of propranolol was lower in the younger age group compared with older age group (2.71 and 3.27 L/h/kg, respectively). Based on geometric CV% values, inter-individual variability in the key propranolol PK parameters was notably higher in the older age group (72.4% to 103%) than in the younger age group (27.5% to 32.9%). Plasma exposure to the 4-OH propranolol metabolite assessed by the $AUC_{0\text{-}9\ h}$ accounted for approximately 6% and 3% of the parent compound in the younger and older age groups, respectively.

The submission included a PPK analysis, based on data from Study 102, aimed at describing the PK of propranolol in infants and evaluating the between-subject variability in the PK of propranolol. The PPK analysis included 166 non-zero observations of propranolol concentrations from 22 patients (10 in Group 1 and 12 in Group 3) sampled twice during the titration period (1 to 2 mg/kg) and 6 times during the fixed dose (target dose 3 mg/kg) period. A one compartment PK model with a first order absorption of drug from an oral dosing compartment and a first order elimination from the central compartment described the PK of propranolol in infants. Irrespective of age group, the between-subject variability for apparent plasma clearance (CL/F) was estimated to be approximately 40%.

In the PPK covariate analysis, a statistically significant effect of body weight on propranolol CL/F was identified, with CL/F increasing with body weight according to an allometric function. Body weight was shown not to affect the apparent volume of distribution (Vd/F). The geometric mean values of the individual predicted CL/F results using the final model were 16.3 L/h and 24.3 L/h for infants from Groups 1 and 2, respectively. The predicted geometric mean CL/F values for Groups 1 and 2 were similar to the observed geometric mean CL/F values (15.2 and 25.5 L/h, respectively). The similarity of the predicted and observed geometric means for CL/F indicates good fit of the final model to the observed data. The PPK analysis supports dosing based on mg/kg rather than on age. In a post hoc analysis, the simulated median Cmax (together with the 5th and 95th percentiles) was 67.1 ng/mL (25.9, 138) for the 9 h interval between doses, and 61.2 ng/mL (23.6, 128) for the 12 h interval between doses.

Pharmacodynamics

There were no studies in the submission investigating the potential pharmacodynamic effects of propranolol in infants with IH.

Dosage selection for the pivotal studies

Study 201 is the pivotal efficacy and safety study. The sponsor states that the choice of doses and regimens was discussed with the European Medicines Agency (EMA) and the FDA. The propranolol doses used in the original observations of efficacy of propranolol in infants with IH were 2 or 3 mg/kg/day and the mean durations of propranolol treatment in the series were 6.1 and 6.8 months (Leauté-Labrèze et al., 2008[38]; Sans et al., 2009[39]). The EMA and FDA recommended that there should be at least a 3 fold difference in doses studied since an investigation of smaller dose increments (for example, 1 to 2 mg/kg/day and 2 to 3 mg/kg/day) was not appropriate considering the widely known logarithmic pharmacological sigmoid dose response curve for propranolol and its receptor. The EMA also recommended that different treatment durations should be studied. After further discussion, it was agreed that the study would investigate two doses (1 and 3 mg/kg/day) over two durations (3 and 6

[38] Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *NEJM* 2008:Jun 12;358(24);2649-2651.
[39] Sans V et al. Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics* 2009: Sep;124(3);e423-431.

months). The proposed doses were within the ranges of doses reported to be effective in the treatment of IH, and doses recommended for propranolol in cardiovascular diseases.

Evaluator comment: The selection of dose for the pivotal study is considered to be acceptable. The approved Australian PI for propranolol tablets recommends (as a guide) propranolol 0.25 to 0.5 mg/kg three or four times daily as required for children with cardiac dysrhythmias, phaeochromocytoma, thyrotoxicosis, and up to 1 mg/kg repeated 3 to 4 times daily as required for Fallot's tetralogy, and 10 mg once or twice daily initially for migraine, increasing to 2 mg/kg in divided doses.

Efficacy

Studies providing efficacy data

The submission included two studies providing clinical efficacy data for the oral propranolol HCl solution (3.75 mg/mL) for the treatment of IH in infants (see Table 3, below). The pivotal efficacy study was V00400 SB 2 01 (referred to as Study 201), and supportive efficacy data were provided by Study 102 (the primary objective of this study was assessment of the steady state PK of propranolol).

Table 3: Study design and data sets for clinical Studies 102 and 201.

Study No.	Design	Sites	Treatment (BID)	Treatment Duration	Total no. of Patients[1]	Analyzed for Efficacy[1]
V00400 SB 1 02	Multicenter, open-label, repeated dose, PK study.	4 in France	V0400SB 3 mg/kg/day	3 months	23	23
V00400 SB 2 01	Multicenter, randomized, double-blind, placebo-controlled, multiple-dose, adaptive Phase II/III study to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo.	55 in 16 countries world-wide	V0400SB 1 mg/kg/day followed by placebo	3 months + 3 months	98	41
			V0400SB 1 mg/kg/day	6 months	102	40
			V0400SB 3 mg/kg/day followed by placebo	3 months + 3 months	100	39
			V0400SB 3 mg/kg/day	6 months	101	**101**
			Placebo	6 months	55	**55**

BID: twice a day; up-titration from Day 0 to 14. Received at least one dose of study treatment (and analysed for safety for both studies). Intent to treat data sets. Stage 1+2 without overrun for Study 201: 2 regimens in bold were the only 2 planned regimens to be compared together for the primary efficacy analysis.

In addition to the primary data analysis at Week 24 (presented in the submitted Clinical Study Report, CSR), the pivotal study also includes an on-going, open-label extension period for an additional 72 weeks, with visits at Weeks 26, 48, 72 and 96 for patients who have completed 24 weeks of double-blind treatment. During the extension period, data will be collected on maintenance of efficacy in patients no longer being treated, and on patients for whom IH has recurred and the investigator considers re-treatment to be appropriate. The *Summary of clinical efficacy* included preliminary Week 48 data on 323 patients who had entered the 72 week extension period. The 72 week extension is still ongoing and the sponsor states that full results will be available in the second quarter of 2014. In addition to the submitted CSR for the pivotal study the preliminary Week 48 data from the on-going 72 week extension period has been reviewed by the clinical evaluator.

Evaluator's conclusions on efficacy

The sponsor states that the efficacy analysis was based on a total of 1333 patients (23 in Study 102, 456 in Study 201, 159 analysed in the CUP, and 695 in the key publications). However, it is considered that, for regulatory purposes, only the efficacy data from the pivotal

Phase II/III study (Study 201) are relevant for evaluating the efficacy of propranolol at the proposed dose for the proposed indication. In this study 460 patients were randomised 1:2:2:2:2 to placebo or one of four propranolol oral solution treatment regimens (1 mg/kg/day for 3 months, 1 mg/kg/day for 6 months, 3 mg/kg/day for 3 months, or 3 mg/kg/day for 6 months). The study included infants aged from 35 to 150 days (inclusive) with facial and non-facial IHs (largest diameter of at least 1.5 cm). The IHs treated in the pivotal study can be considered to be low-risk as infants were excluded if they had one or more life-threatening IHs, function threatening IHs, or complicated ulcerated IHs. In addition, in the total population the IH complication rate over the duration of the study assessed on-site by the investigators was low, suggesting low-risk disease. The study excluded patients who had received previous medical or surgical treatment for IHs.

The pivotal study had an adaptive design allowing for the modification of key elements based on the results of an interim analysis (that is, increased sample size, selection of best propranolol treatment regimen or regimens, stop for futility or safety) with control of the pre-specified Type I error[40]. The interim analysis was undertaken by an Independent Data Monitoring Committee (IDMC) and included data on 190 randomised patients of whom 188 patients from the five treatment arms had completed Week 24 (or had been prematurely withdrawn from treatment). Based on the results of the interim analysis, the IDMC recommended that the trial continue with one single active treatment arm (3 mg/kg/day for 6 months) to be compared with placebo in the primary efficacy analysis at Week 24, no sample size adjustment/re-estimation, and all patients being kept in their initial randomisation arm. Accrual in the study continued while the interim analysis was being undertaken, and the planned sample size had been reached with 460 patients randomised before the IDMC recommendations were made.

The primary pre-specified efficacy endpoint was the proportion of subjects achieving complete or nearly complete resolution of the target IH at Week 24, assessed by centralised (blinded) reading of photographs, in the ITT population. The proportion of subjects achieving this endpoint was markedly higher in the propranolol 3 mg/kg/day arm than in the placebo arm, and the difference between treatment arms was statistically significant (60.4% (61/101) versus 3.6% (2/55), respectively, $p < 0.0001$). The results of the primary analysis were supported by sensitivity analyses in the per protocol (PP) data set, and the ITT date set using a re-defined primary efficacy endpoint. In addition, logistic regression analysis of the primary efficacy endpoint, adjusted for the stratification factors and the randomisation ratio, statistically significantly favoured propranolol 3 mg/kg/day for 6 months compared with placebo ($p < 0.0001$). The observed placebo success rate of 3.6% was lower than the estimated rate on which the sample size calculations was based (10%), while the active treatment rate of 60.4% was higher than the estimated rate (55%).

The results for complete or nearly complete resolution of IH at Week 24 based on the photographic data assessed by 2 centralised readers differed markedly from the results for this outcome based on on-site investigator clinical assessment. Based on investigator assessment, complete or near complete resolution of the target IH at Week 24 compared with baseline was 10.5% (2/19) in the placebo arm and 26.7% (24/90) in the propranolol 3 mg/kg/day for 6 months arm, nominal $p = 0.4419$. Complete resolution as assessed by the investigator occurred in no patients in the placebo arm at any visit between Day 7 and Week 24. In the 3 mg/kg/day 6 months arm, complete resolution as assessed by the investigator occurred in only 7 (7.8%) patients at Week 24 (5 patients, 5.6% without sequelae; 2 patients, 2.2%, with minimal sequelae; and no patients with marked sequelae). The difference in complete/nearly complete resolution rate between the two treatment arms based on investigator assessment was not statistically significant at any visit.

[40] A Type 1 error describes the probability of rejecting the null hypothesis (hypothesis that no change will occur) when it is true; or a 'false positive' finding.

In the 3 mg/kg/day for 6 months arm, centralised assessment identified 38 patients with complete/nearly complete resolution who were not assessed as complete/nearly complete resolution by investigator assessment, and 1 patient who was assessed as complete/nearly complete resolution by investigator assessment but not by centralised assessment. Sixty-two (62) patients were consistently assessed by centralised and investigators assessments, 23 as complete/nearly complete resolution and 39 as not complete/nearly complete resolution (see Table 4, below).

Table 4: Study 201. Consistency between centralised and on-site investigator assessments of complete/nearly complete resolution of IH.

Complete/nearly complete resolution		Placebo (n=55)	V0400SB 3 mg/kg/day 6mths(n=101)
Centralized assessment (primary endpoint)	Investigator assessment		
Yes	Yes	0	23
Yes	No	2	38
No	Yes	0	1
No	No	53	39

The sponsor notes that the results of the investigator assessment of complete/nearly complete resolution of IH at Week 24 'clash strikingly' with the results of the centralised assessment, but considers that comparison of the two different assessment methods is 'of limited significance' due to the dissimilarity between the methods used to assess the outcome. The sponsor states that assessment of complete/near complete response performed by two expert readers was used as the primary criterion in order to ensure both independence and reproducibility of assessments, and only took in to account the comparison of Week 24 photographs with baseline (Week 0) pre-treatment photographs. In contrasts, the investigators' assessment of the same criterion was by definition subject to greater heterogeneity (56 investigating sites versus 2 expert readers), less reproducibility (no training for this parameter, no validation of intra/inter reader reproducibility) and was also methodologically different since it was based on direct visual examination of the patient at Week 24 compared with the Week 0 photographs and additional medical data available at the investigator site arising from clinical examination of the patient.

However, in contrast to the sponsor's opinion it is considered that the difference between the two assessment methods as regards complete/nearly complete resolution of IH at Week 24 is a significant matter and should not be dismissed lightly. The investigators were required to undertake a detailed clinical assessment of the target IH at each visit, and the nature of this examination is considered to be consistent with that which would be undertaken in clinical practice and on which clinical decisions regarding treatment would be made. Furthermore, it can be reasonably assumed that the investigators chosen to contribute patients to this study would be physicians experienced in the assessment and management of infants with IH. Consequently, it is considered that it would be unwise to discount the clinical opinion of these physicians as regards complete or nearly complete resolution of IH. In addition, there is no evidence that the criteria used to determine complete/nearly complete resolution of IH based on photographic assessment has been validated against the same outcomes determined by clinical examination by experienced physicians.

Overall, it is considered that the inconsistency between the two assessment methods raises more doubts about the reliability of photographic assessment of complete/incomplete resolution rather than about on-site investigator assessment. Furthermore, the striking inconsistency between the two assessment methods raises significant uncertainty about the true effect of the propranolol 3 mg/kg/day for 6 months regimen on complete/nearly complete resolution compared with placebo.

In contrast to the uncertainty concerning complete/nearly complete resolution, it is considered that the data from the pivotal study suggest that propranolol 3 mg/kg/day for 6 months results in improvement in IH at Week 24 compared with placebo. However, the

evidentiary weights given to these data are limited as all secondary efficacy endpoints up to and including Week 24 were exploratory and p-values for the analyses of these endpoints were all nominal rather than confirmatory. The exploratory data suggesting that propranolol 3 mg/kg/day for 6 months improves IH compared with placebo are summarised in the following two paragraphs.

In the centralised assessment, quantitative assessment of reduction in IH surface area, reduction in maximal IH diameter, and change in colour of the IH from baseline to Week 12 and Week 24 favoured propranolol 3 mg/kg/day for 6 months compared with placebo, and the changes were nominally statistically significant for surface area and colour. In the centralised assessment, improvement in the target IH at Week 5 was observed in a greater percentage of patients in the propranolol 3 mg/kg/day arm than in the placebo arm (88.0%, 88 patients versus 5.4%, 2 patients, respectively). Further improvements in the propranolol 3 mg/kg/day for 6 months versus placebo arm for the following pairs of visits were, respectively, 13.8% versus 3.8% for Week 8 versus Week 5; 9.2% versus 4.2% for Week 12 versus Week 8; 10.5% versus 4.8% for Week 12 versus Week 16; 2.2% versus 0% for Week 20 versus Week 16; and 4.5% versus 0% for Week 24 versus Week20. Furthermore, between Week 5 and Week 24, global improvement from baseline (that is, at least one assessment of improvement between paired visits without any worsening) was 73.0% (73 patients) in the 3 mg/kg/day arm and 5.5% (3 patients) in the placebo arm, nominal $p < 0.0001$.

In addition, centralised, investigator and parent/guardian assessments all showed greater sustained improvement in IH (Kaplan Meier (KM) estimates) at Week 5 and Week 24 in the 3 mg/kg/day arm than in the placebo arm. In the centralised assessment, sustained improvement was observed at Week 5 in 72.7% (72 patients) of patients in the 3 mg/kg/day arm and 5.4% (2 patients) in the placebo arm, with the corresponding results for the two treatment arms at Week 24 being 79.5% (77 patients) and 9.0% (3 patients), respectively. In the investigator assessment, sustained improvement was observed at Week 5 in 70.9% (68 patients) of patients in the 3 mg/kg/day arm and 20.1% (10 patient) in the placebo arm, with the corresponding results for the two treatment arms at Week 24 being 82.5% (76 patients) and 32.4% (12 patients), respectively. In the parent/guardian assessment, sustained improvement was observed at Week 5 in 67.4% (64 patients) of patients in the 3 mg/kg/day arm and 19.9% (10 patients) in the placebo arm, with the corresponding results for the two treatment arms at Week 24 being 85.6% (76 patients) and 45.0% (14 patients), respectively. For the three assessments, the difference in the KM estimates of time to first sustained improvement (Week 5 first assessment time-point) of the target IH over the 24 weeks of the study favoured active treatment over placebo, nominal $p < 0.0001$.

Data suggesting that the IHs in the pivotal study were low-risk come from the infrequently occurring target IH complications in the total patient population, qualitatively assessed on-site by the investigators. Functional impairment due to the target IH occurred (or persisted in 1 case) on study treatment in 7 patients (3 [5.5%] in the placebo arm, and 4 [1.0%] in the combined propranolol arms). Ulceration of the target IH occurred on treatment in 13 patients (2 [3.6%] in the placebo arm and 11 [2.7%] in the combined propranolol arms). Bleeding/haemorrhaging of the IH occurred in 7 patients (1 [1.8%] in the placebo arm and 6 [1.5%] in the combined propranolol arms), and in all cases were pre-existing or occurred early in treatment (before or at Day 21). In all cases (apart from 1) the bleeding/haemorrhaging resolved at Week 5 at the latest.

The submitted data included preliminary data on patients from the pivotal study who have entered the 72 week open-label extension phase after completing the 24 week double blind treatment period. Of the patients in the 3 mg/kg/day 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at Week 48 (based on centralised assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The results showed that complete/nearly complete resolution at Week 24 can be maintained through to Week 48 in patients treated with propranolol 3

mg/kg/day (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution in the placebo arm actually increased from Week 24 to Week 48 (3.6%, 2/55 to 31.6%, 6/19). The preliminary results also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day for 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment but before Week 48, compared with 5.3% (1/19) of patients in the placebo arm.

In summary, it is considered the evidence from the pivotal study showing a markedly increased rate of complete/nearly complete resolution in IH at Week 24 compared with placebo, based on centralised assessment (blinded) by two readers (primary efficacy endpoint), is unreliable due to the striking difference in this outcome when assessed (blinded) on-site by the study investigators (secondary exploratory efficacy endpoint). However, the efficacy data from the pivotal study suggest that propranolol 3 mg/kg/day for 6 months can improve low-risk IH compared with placebo when assessed at Week 24, but the pivotal study was not designed to assess improvement, all data were exploratory, and all p-values were nominal rather than confirmatory. There is low level evidence from the CUP and the published data reviewed by the sponsor that propranolol can improve IH outcomes, but little regulatory weight can be given to this predominantly observational evidence.

Safety

Studies providing evaluable safety data

The primary safety analysis in the submission includes pooled safety data on 424 patients from Studies 102 (n = 23) and 201 (n = 401) treated with the sponsor's oral propranolol preparations. Additional safety analyses in the submission included:

- sponsor's Study 301, an on-going, open-label study of propranolol in infants with proliferating IH, reporting serious adverse events (SAEs) in 1 patient in the 11 enrolled up to the cutoff date of 31 December 2012;
- cumulative data from 660 patients with IH (including high-risk disease) from the sponsor's French CUP treated between 13 April 2010 and the cutoff date of 12 October 2012; and
- studies and individual case reports of 1367 patients with IH (including high-risk disease) treated with oral propranolol presented in 60 publications from the scientific literature reviewed by the sponsor.

In total, the safety data provided in the submission included 1084 patients treated with the sponsor's oral propranolol preparations (424 pooled from studies 102 and 201, 660 in the French CUP), and 1367 patients from the scientific literature treated with other preparations of propranolol.

The sponsor stated that, '*based on the pre-New Drug Application (NDA) meeting with the FDA, on 26 [April] 2012, and the [pre-submission] meeting with the EMA on 29 [November] 2012, it was agreed that, in order to obtain the fullest possible sample size for this submission, all the above listed sources of data were to be used for this analysis of the safety of oral propranolol in the treatment of IH. It was also agreed that the CUP data should be presented in [the dossier] Section on Post-Marketing Data. Moreover, the FDA agreed that it was appropriate to prepare a unique [integrated safety summary, ISS] documen*t'.

In the TGA clinical evaluation report (CER), the evaluation of safety primarily focuses on the data from the pivotal Phase II/III study (201), and the pooled safety data from Studies 201 and 102 reported in the ISS/SCS. There is considerable overlap between the safety data for propranolol from the pivotal study and the pooled safety data reported in the ISS/SCS. This is to be expected as the 424 propranolol treated patients in the pooled safety population

included 401 (94.6%) patients from pivotal Study 201. Therefore, the pooled safety data for propranolol is primarily driven by the safety data from Study 201. In addition, the safety results from the CUP have been considered, and brief mention of the data from the scientific literature reviewed by the sponsor has been provided.

Patient exposure

In the pivotal study safety population and the pooled safety population, actual extent of exposure was defined as the range of the days for which the patient was exposed to treatment (that is, date of last intake of the drug (end of treatment, EOT) minus date of first intake of the drug plus 1 day). In the pivotal study, the data did not distinguish between propranolol for 3 months followed by placebo for 3 months (that is, the data are described as 1 mg/kg/day for 3 months and 3 mg/kg/day for 3 months). In the pivotal study, all 5 treatment arms can be compared during the titration period (Day 0 to Day 21), then due to attrition in the placebo arm the 4 active treatment arms can be compared over the Day 21 to Week 12 period, and after Week 12 the two active, 6 month treatment arms can be directly compared. The extent of exposure for the patients in the safety set from the pivotal study is summarised below in Table 5.

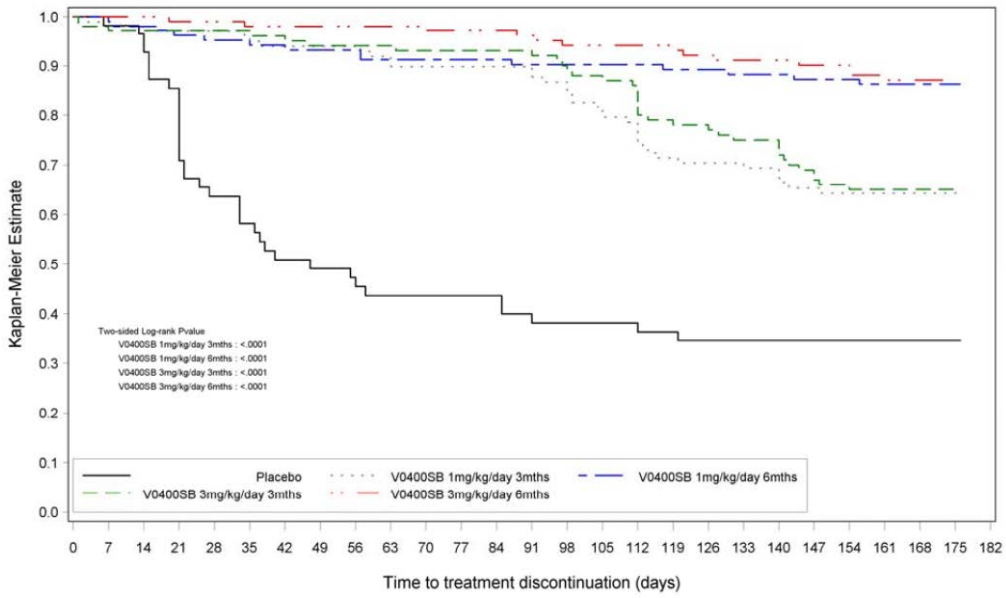
Table 5: Study 201. Extent of exposure; safety set.

	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)	Total (N = 456)
Extent of exposure*(in days)						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
Mean (SD)	82.60 (67.31)	142.74 (43.73)	156.92 (39.89)	146.61 (38.45)	160.97 (26.59)	143.55 (48.32)
Q1 Q2 Q3	21.00 47.00 168.00	113.00 168.00 169.00	168.00 168.00 169.00	135.50 167.50 169.00	167.00 168.00 169.00	141.00 168.00 169.00
min max	6 176	1 214	7 220	7 176	19 190	1 220

** Estimated day of end of treatment (EOT) - day of first treatment administration + 1*

Treatment discontinuations over time in the pivotal study safety set are summarised below in Figure 2 by KM survival curves.

Figure 2: Study 201: Treatment discontinuation over time, Kaplan Meier survival curves for time to treatment discontinuation; safety set.



In the pooled safety population, the actual exposure data were analysed using two different data sets derived from the total pooled safety population, which included 424 propranolol treated patients (401 patients from the four active treatment arms in the pivotal Phase II/III Study 201 and 23 patients from the Phase I open label Study 102 of propranolol 3 mg/kg/day for 3 months) and 236 placebo treated patients from the pivotal study).

One analysis compared all placebo (n = 236), all propranolol 1 mg/kg/day (n = 200), all propranolol 3 mg/kg/day (n = 224), and all propranolol (n = 424). In this analysis, the safety results for the placebo and active treatment components for the two 3 months of active (1 mg/day and 3 mg/day) followed by 3 months of placebo regimens were separated. Therefore, in this analysis the all placebo group (n = 236) was derived from the pivotal Study 201 and included 55 patients from the placebo for 6 months regimen, 88 placebo treated patients from the second 3 month phase of the 1 mg/kg/day 3 months regimen, and 93 placebo treated patients from the second 3 month phase of the 3 mg/kg/day 3 months regimen. The all propranolol 1 and 3 mg/kg/day groups included patients from the pooled regimens treated for 3 or 6 months; that is all 1 mg/kg/day group (n = 200) included 102 patients from the 6 months regimen and 98 patients from the 3 months regimen; all 3 mg/kg/day group (n = 224) included 101 patients from the 6 months regimen and 123 patients from the 3 month regimens.

One analysis compared placebo for 6 months (n = 55), propranolol 1 mg/kg/day for 3 months (n = 98), propranolol 1 mg/kg/day for 6 months (n = 102), propranolol 3 mg/kg/day for 3 months (n = 123), propranolol and propranolol for 6 months (n = 101), and the total population (n = 479).

Evaluator comment: In the pivotal study, the mean duration of exposure in the placebo arm was about half that of the 3 mg/kg/day 6 months arm (that is, 83 versus 161 days, respectively). Interpretation of the safety findings need to take into account the difference in treatment exposure among the placebo and active treatment arms. Differences in extent of exposure between placebo and active treatment are explained by the differences in premature treatment discontinuation rates, with most of the patients remaining on study treatment as long as they were on active treatment. In the randomised data set (pivotal study), 36 (65.5%) patients discontinued treatment prematurely in the placebo arm compared with 14 (13.7%) patients in the 3 mg/kg/day 6 months arm, and the number of patients discontinuing due to treatment inefficacy in the two arms was 32 (58.2%) and 9 (8.8%), respectively. In the placebo arm, treatment discontinuation started early (as soon as Week 2), with a very steep decrease between Week 2 and Week 5, with 49.1% (27/55) of the patients having prematurely discontinued treatment at Week 5 and 65.5% (36/55) at Week 20. In contrast, in the 3 mg/kg/day 6 months arm, only 2.9% (3/102) of patients had discontinued prematurely at Week 5 and 11.8% (12/101) at Week 20.

Post marketing data

The dossier also included 5 six monthly safety reports, covering the period from 13 April 2010 to 12 October 2012, prepared by the sponsor and submitted to the French Competent Authority, relating to temporary authorisation for use (ATU) of oral propranolol (3.75 mg). The first ATU was approved in France on 13 April 2010, and the therapeutic indication was proliferating IHs which are life threatening or give rise to a functional risk, and ulcerative hemangioma not responding to simple treatment in infants unable to be included in a clinical trial. France is the only country for which patient safety data have been received by the sponsor. The integrated summary of safety/ summary of clinical safety (ISS/SCS) included a summary of the data from the ATU reports (as did the sponsor's clinical overview).

Scientific literature

The ISS/SCS included a review undertaken by the sponsor of the AE data from 60 publications involving 1367 patients treated with propranolol for IH. The sponsor noted that there were very few details in the literature regarding how the formulation of off-label, oral propranolol was manufactured. No publications relating to the use of the proposed Pierre Fabre formulation, oral solution formulation of propranolol, were identified. The majority of patients reported in the publications were treated with propranolol 2 mg/kg/day (range 1-4 mg/kg/day) for up to 30 months, except for 3 patients reported in one publication who received higher doses (3-6 mg/kg/day).

Evaluator's conclusions on safety

Number of patients with safety data

The safety data provided in the submission included information on a total of 2,451 patients with IH treated with propranolol (424 patients from the clinical trial program, 660 patients from the French CUP, and 1367 from the scientific literature identified by the sponsor). The key safety data are considered to be from the pivotal study, which included 456 patients in the safety set aged between 35 and 150 days at inclusion with proliferating IH requiring systemic therapy (401 patients in the propranolol arms, and 55 patients in the placebo arm).

Exposure to propranolol

In the pivotal study, the mean duration of treatment in the 3 mg/kg/day, 6 months arm was approximately 2 fold greater than in the placebo arm (that is, 161 days [range: 1, 220 days] versus 83 days [range: 6, 176 days]), and similar patterns were observed between the placebo arm and each of the other three active treatment arms. The pattern of increased length of treatment in the active arms compared with the placebo arm reflects the lower rate of permanent treatment discontinuations in the active arms compared with the placebo arm, due primarily to differences relating to discontinuations due to inefficacy. In the placebo arm, permanent treatment discontinuation due to inefficacy was approximately 6.6-fold higher than in the 3 mg/kg/day 6 months arm (58.2% versus 8.8%, respectively).

In the clinical trial program, a total of 155 patients have been exposed to propranolol for ≥ 24 weeks (74 in the 3 mg/kg/day 6 months arm, 80 in the 1 mg/kg/day 6 months arm, and 1 in the 1 mg/kg/day 3 months arm). The clinical trial exposure numbers are small but adequate given the safety data from the CUP and the scientific literature relating to the use of propranolol in children with IH. In addition, reassurance is provided by the extensive exposure to propranolol in adults, and the absence of safety signals in children suggesting that the safety profile of the drug will be significantly different in children and adults.

Treatment-emergent adverse events

Treatment emergent adverse events (TEAEs) occurred notably more commonly in propranolol treated patients than in placebo treated patients, despite the difference in the length of treatment between the two treatment groups. In the pooled safety population, TEAEs were reported in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 versus 88.8%, 199/224, respectively).

TEAEs reported in at least 10% of patients in the all propranolol group (n = 424) versus the all placebo group (n = 236) were (in descending order of frequency in the active arm): nasopharyngitis (23.6% versus 15.3%); pyrexia (21.2% versus 7.2%); diarrhoea (18.9% versus 3.4%); teething (15.3% versus 9.3%); cough (11.8% versus 7.2%); vomiting (10.6% versus 3.4%); and upper respiratory tract infection (URTI, 10.1% versus 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day 6 months arm (n = 101) versus the placebo arm (n = 55) were (in descending order of frequency in the active arm): nasopharyngitis (33.7% versus 18.2%); diarrhoea (27.7% versus 7.3%); pyrexia (26.7% versus 9.1%); teething (20.8% versus 10.9%); bronchitis (16.8% versus 1.8%); URTI (13.9% versus 7.3%); vomiting (12.9% versus 5.5%); cough (11.9% versus 7.3%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); bronchiolitis (8.9% versus 5.5%); dermatitis diaper (8.9% versus 3.6%); toothache (8.9%, 8/101 versus 3.6%); conjunctivitis (7.9% versus 3.6%); vaccination complication (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); middle insomnia (5.0% versus 5.5%); nightmare (5.0% versus 1.8%); and rash (5.0% versus 1.8%).

In the pivotal study, TEAEs reported in at least 2% of patients in the 3 mg/kg/day 6 months arm and occurring at least 3 fold more commonly than in the placebo arm were considered to be clinically significant. The events meeting this criteria (3 mg/kg/day 6 months [n = 101] versus placebo [n = 55]) were: diarrhoea (27.7% versus 7.3%); bronchitis (16.8% versus 1.8%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); sleep disorder (6.9% versus 1.8%); ear infection (4.0% versus 0%); pharyngitis (3.0% versus 0%); viral infection (3.0% versus 0%); gastro-oesophageal reflux disorder (GORD, 3.0% versus 0%); and aspartate transaminase (AST) increased (3.0% versus 0%).

In the pivotal study, the majority of TEAEs were reported to be mild or moderate in intensity, to have occurred before or at Week 12 (that is, before switch to placebo in the 1 and 3 mg/kg/day 3 months treatment arms), and to have resolved by Week 24.

Treatment related treatment emergent adverse events

In the pooled safety population, treatment related TEAEs were reported more frequently in patients in the all propranolol group than in all placebo group (36.3%, 154/424 versus 14.8%, 35/236). Treatment related TEAEs occurring in at least 2% of patients in the all propranolol group (n = 424) and/or the all placebo group (n = 236) were (respectively) in descending order of frequency in the active treatment group: peripheral coldness (7.1% versus 0%); diarrhoea (5.4% versus 1.3%); sleep disorder (5.0% versus 0.8%); middle insomnia (4.7% versus 1.7%); nightmare (4.2% versus 1.7%); vomiting (2.6% versus 0.4%); constipation (2.4% versus 0.4%); decreased appetite (2.4% versus 0%); somnolence (2.4% versus 0%); restlessness (2.1% versus 0.8%); hypersomnia (2.1% versus 0.4%); and insomnia (1.4% versus 2.1%). Four (4) patients experienced severe treatment related TEAEs: 1 with nightmare in the 1 mg/kg/day 6 months arm; 1 with increased serum alkaline phosphatase level in the active treatment phase of the 3 mg/kg/day 3 months arm; and 2 patients with aggravated condition (1 in the placebo group, and 1 in the active treatment phase in the 3 mg/kg/day 3 months arm).

In the pivotal study, 34.7% (35/101) of patients in the 3 mg/kg/day 6 months arm experienced at least one treatment related TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day 6 months arm (n = 101) and/or the placebo arm (n = 55) were (in decreasing order of frequency in the active treatment arm): peripheral coldness (8.9% versus 0%); diarrhoea (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); nightmare (5.0% versus 1.8%); middle insomnia (4.0% versus 5.5%,); vomiting (3.0%, versus 1.8%); aspartate transaminase (AST) increased (3.0% versus 0%); insomnia (3.0% versus 5.5%); rash (2.0% versus 0%); blood potassium increased (2.0% versus 0%); and frequent bowel movements (1.0% versus 3.6%).

Deaths and other serious adverse events

There were no deaths in the pooled safety population. However, there was 1 (0.15%) death in the CUP reported in 660 patients (complete heart atrioventricular (AV) block and acute cardiac failure) considered by the sponsor and French health authority to be of doubtful

relationship to treatment considering that cardiac safety measures had been initiated following the introduction of propranolol, the nature of the underlying non-cardiac disease, and the numerous concomitantly taken medications.

In the pivotal study, SAEs were reported in 5.5% (3/55) of patients in the placebo arm (3 events), 5.1% (5/98) of patients in the 1 mg/kg/day 3 months arm (5 events), 2.9% (3/102) of patients in the 1 mg/kg/day 6 months arm (5 events), 9.0% (9/100) patients in the 3 mg/kg/day 3 months arm (13 events), an 5.9% (6/101) patients in the 3 mg/kg/day 6 months arm (7 events). The proportion of patients with SAEs was similar in the placebo and propranolol 3 mg/kg/day 6 months arms (5.5% versus 5.9%, respectively). No dose dependent relationship for SAEs was observed for the 4 propranolol treatment regimens.

Of the 33 SAEs reported in the pivotal study, 26 occurred in 401 patients while on active treatment with propranolol (0.06 events per patient) and 7 occurred in 236 patients while on treatment with placebo (0.03 events per patient). The most commonly reported SAEs were condition aggravated, drug ineffective and bronchiolitis each in 3 patients, and bronchiolitis in 2 patients, all other SAEs occurred in 1 patient each. SAEs led to temporary treatment discontinuation in 8 patients and permanent treatment discontinuation in 9 patients. All patients recovered from their SAEs, except for 2 patients who recovered with sequelae after permanently discontinuing the study drug (epilepsy and condition aggravated).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1 of condition aggravated in 1 patient in the placebo arm; 1 of AV block second degree (Mobitz I type) in the active treatment phase in the 1 mg/kg/day 6 months arm; 1 of obstructive bronchitis in the active treatment phase in the 3 mg/kg/day 3 months arm; 1 of condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day 3 months arm; and 1 of bradycardia in the active treatment phase in the 3 mg/kg/day 3 months arm. The only one of the 5 events not categorised as a sudden unexpected serious adverse reaction (SUSAR) was bradycardia.

The submission also provided SAE data from the pivotal study reported post Week 24 at the cut-off date of 31 December 2012. In this period, 319 patients had entered the cut-off phase and 20 (6.3%) patients had experienced at total of 30 SAEs. There were no unexpected SAEs in the preliminary data from the post-Week 24 extension phase of the pivotal study. One (1) patient from on-going study (301) enrolling previously treated patients from studies 102 and 201 had experienced 1 SAE (bronchiolitis).

Permanent treatment discontinuation and other significant adverse events

Treatment emergent AEs resulting in permanent treatment discontinuation occurred more commonly in patients treated with propranolol than in patients treated with placebo. In the pooled safety population, TEAEs resulting in permanent treatment discontinuation were reported in 4.7% (11/236) of patients in the all placebo group compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent study drug discontinuation in more than 1 patient in the combined all placebo and all propranolol groups were: condition aggravated in 4 patients (3 [1.5%] in the all placebo group, and 1 [0.2%] in all propranolol group); drug ineffective in 3 patients (2 [0.8%] in the all placebo group, and 1 [0.2%] in the all propranolol group); and bronchiolitis in 3 patients (2 [0.8%] in the all placebo group, and 1 [0.2%] in all propranolol group).

In the pivotal study, TEAEs resulting in permanent treatment discontinuation were reported in 6 (10.9%) patients in the placebo arm (7 events), 4 (4.1%) patients in the 1 mg/kg/day 3 months arm (4 events), 2 patients in the 1 mg/kg/day 6 months arm (2 events), 7 (7.0%) patients in the 3 mg/kg/day 3 months arm (9 events) and 3 (3.0%) patients in the 3 mg/kg/day 6 months arm (3 events). The proportion of patients discontinuing treatment due to permanent TEAEs was greater in the placebo arm than in the 3 mg/kg/day 6 months arm (10.9% versus 3.0%, respectively). No dose dependent relationship for TEAEs resulting in

permanent treatment discontinuation was observed for the 4 propranolol treatment regimens.

Dose reductions due to TEAEs were reported in 4 patients in clinical trial program (3 in propranolol treated patients and 1 in a placebo treated patients), and temporary treatment discontinuations due to TEAEs were reported in 63 patients (58 in propranolol treated patients and 6 in placebo-treated patients).

Important identified risks associated with propranolol

Important risks in infants with IHs treated with propranolol include bradycardia, intensification of AV block, hypotension, hypoglycaemia (including related seizures); bronchospasm, and bronchial hyper-reactivity reactions.

The most frequently observed important risks observed with propranolol related to bronchospasm and bronchial hyper-reactivity reactions. In the pooled safety population, TEAES of bronchospasm and bronchial hyper-reactivity reactions were reported in 86 (20.3%) out of 424 propranolol treated patients. Of these 86 patients, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%) had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 16 (2.4%) of 660 patients experience these reactions.

In the pooled safety population, TEAEs of hypotension were reported 5 (1.2%) out of 424 propranolol treated patients. Three (3) cases were observed in all 1 mg/kg/day group at 3 weeks, 2 months and 2.5 months, and 2 cases were observed during the titration phase in the 3 mg/kg/day 3 months regimen. All 5 events were reported before or at W12. All were asymptomatic, all were of mild intensity, none was a SAE, and none required corrective treatment or dose adjustment. All were considered by the investigator to be possibly related to treatment with the study drug. In the CUP 2 (0.3%) of 660 patients experienced hypotension.

In the pooled safety population, TEAEs of bradycardia were reported in 2 out of 424 (0.5%) propranolol treated patients, and both were considered by the investigator to be related to the study drug. Both patients had been participants in the pivotal study, 1 (1.0%) in the 1 mg/kg/day 6 months arm (after Week 12, on Day 167), and 1 (1.0%) in the 3 mg/kg/day 3 months arm (before or at Week 12, on Day 7) considered to be a SAE and resulting in permanent treatment discontinuation. In the CUP, 2 (0.3%) of 660 patients were each reported to have experienced bradycardia (serious adverse drug reactions, ADRs).

In the pooled safety population, 1 (0.2%) out of 424 propranolol treated patients experienced a TEAE of intensification of AV block following the first dose of propranolol (0.5 mg/kg/day) considered by the sponsor to be possibly related to treatment, and resulting in permanent treatment discontinuation. In the CUP, 1 (0.15%) of the 660 patients experienced complete AV block and fatal heart failure considered to be unrelated to treatment for the reasons provided above under the heading *Death and other serious adverse events*

In the pooled safety population, TEAEs of hypoglycaemia were reported in 2 (0.5%) out of 424 propranolol treated patients. Both events occurred during the titration period at D14, one event at 1 mg/kg/day and one event at 3 mg/kg/day, and both events were of mild intensity (2.5 mmol/L and 2.9 mmol/L, respectively). In 1 patient (2.5 mmol/L) the D14 event had been preceded by gastroenteritis since D11 with vomiting, diarrhoea and poor feeding. No hypoglycaemic symptoms were reported for either case and blood glucose levels normalised spontaneously. In the CUP 4 (0.6%) of 660 patients experienced hypoglycaemia.

Laboratory assessments

Overall, the analysis of haematology and biochemistry laboratory parameters does not give cause for concern or generate new safety signals. The assessment 'blood glucose levels' was specifically targeted in the clinical study program, and was monitored by pin-prick in the

titration period and routinely in venous blood throughout the course of the study. In the pooled safety population, there were no cases in the placebo (n = 55) or all propranolol (n = 424) groups of potentially clinically significant blood glucose values (< 2.22 mmol/L) measured by pinprick at +2 h and +4 h post-dose on the first day of treatment (Day 0) or on both days of increased dose (Day 7 and Day 14) in the titration period. In the pooled safety population, 1 (0.4%) patient in the all placebo group (n = 236) and 1 (0.2%) patient in the all propranolol group (n = 424) with normal baseline blood glucose levels experienced treatment emergent critical blood glucose levels < 2.6 mmol/L detected by routine monitoring of venous blood at Week 24.

Vital signs: Blood Pressure

In the pivotal study, during the titration period, the proportion of patients with systolic blood pressure (SBP) and diastolic blood pressure (DBP) values below the normal range were similar for the placebo group and the grouped 1 mg/kg/day and grouped 3 mg/kg/day regimens. The proportion of patients in the placebo, grouped 1 mg/kg/day and grouped 3 mg/kg/day regimens with SBP values below the normal range during the titration period were 29% (16/55) versus 33.0% (66/200) versus 29.4% (59/201), respectively, and the corresponding results for DBP were 85.5% (47/55) versus 82.0% (164/200) versus 83.1% (167/201), respectively. Over the course of the pivotal study, SBP and DBP values below the normal range were frequently observed in all five treatment arms (SBP: 41.8% in the placebo arm, 50.0% to 53.5% in the active arms; and DBP: 89.1% in the placebo arm, and 87.3% to 97.0% in the active arms). The results show that reductions in BP in the placebo and active treatment arms were predominantly diastolic.

In the pivotal study, almost all very low SBP/DBP potentially clinically significant values (PCSVs, < 50/30 mmHg whatever the age) were DBP values, and occurred during the titration period. The proportion of patients with PCSVs from Day 7-1 h to Day 14-4 h in the titration period was similar for the grouped 3 mg/kg/day regimen and the placebo regimen (14.4%, 29/201, 52 events versus 14.5%, 8/55, 12 events), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200, 20 events). The proportion of patients with PCSVs notably decreased after the titration period in each of the treatment arms.

Vital signs: Heart Rate

In the pivotal study, there was a decrease in heart rate (HR) of about 7 beat per minute (bpm), on-average, from baseline in the propranolol treatment arms during the titration period. In the pivotal study, HR values below the normal range occurring in at least one patient over the course of the study were 14.5% (8/55), 22.4% (22/98), 15.7% (16/102), 17.0% (17/100) and 25.7% (26/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively.

In the pivotal study, low HR PCSVs (< 60 bpm) occurred infrequently in all treatment arms and the rates were 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively.

Vital signs: ECG

No clinically significant ECG abnormalities appear to have been identified by routine monitoring.

Vital signs: Other

No significant differences were observed in the pivotal study between propranolol and placebo treated patients as regards respiratory rate, temperature, head circumference, and weight.

Special groups

The safety patterns were different between the two age groups and the two sexes, but the observed differences are unlikely to be clinically significant and provide no support for dose adjustment based on age or sex.

First Round Benefit-Risk Assessment

First round assessment of benefits

In the pivotal study, the proportion of infants aged from 30 to 150 days achieving complete/nearly complete resolution of proliferating IH requiring systemic therapy at Week 24 was markedly higher in the propranolol 3 mg/kg/day arm than in the placebo arm, based on centralised (blinded) reading of patient photographs in the ITT data set (60.4%, 61/101, versus 3.6%, 2/55, respectively, $p < 0.0001$). The absolute difference between the active and placebo treatment arms (56.8%) indicates that approximately 2 patients need to be treated with propranolol 3 mg/kg/day 6 months in order for 1 of them to show a complete or nearly complete resolution in their IH at Week 24 based on photographic data (that is, number needed to treat [NNT] = 2). However, the results for the primary efficacy analysis for complete/nearly complete resolution of IH at Week 24 are strikingly inconsistent with the results for this outcome based on investigator assessment in the propranolol 3 mg/kg/day 6 months and placebo arms (26.7%, 24/90, versus 10.5%, 2/19, respectively, $p = 0.4419$).

The sponsor claims that the difference between the results for the two assessment methods for complete/nearly complete resolution in IH at Week 24 is insignificant, due to notable differences in the methods used to assess the outcome. However, the difference in outcome between the two methods is considered to be important, and the data from investigator assessment based on clinical examination by physicians experienced in the management of IH cannot be dismissed. In particular, it is considered that the difference in outcome between the two assessment methods raises concerns about the validity of the photographic criteria to satisfactorily identify clinically meaningful complete/nearly complete resolution of IH. Overall, the inconsistency between the evidence for complete/nearly complete resolution of IH at Week 24 from blinded centralised assessment (2 readers) and blinded on-site investigator assessment is considered to raise uncertainty about the true effect of propranolol compared with placebo on this endpoint. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day for 6 months results in clinically significant complete/nearly complete resolution of IH at Week 24 compared with placebo.

It is considered that the pivotal study provides some evidence suggesting that treatment with propranolol 3 mg/kg/day for 6 months might result in clinically meaningful improvement of IH compared with placebo at Week 24. However, it is considered that all evidence suggesting that propranolol 3 mg/kg/day for 6 months provides a treatment benefit relating to improvement at Week 24 is exploratory. The pivotal study was not designed to investigate improvement in outcome in IH between baseline and Week 24, and p values for all secondary efficacy endpoints up to and including Week 24 were nominal rather than confirmatory. Therefore, for regulatory purposes there are no pivotal data establishing that propranolol 3 mg/kg/day 6 months can improve IH compared with placebo at Week 24.

Improvement in the surface area, maximal diameter and colour of the IH from baseline to Week 12 and Week 24 were observed in the propranolol 3 mg/kg/day arm compared with placebo. Global improvement from baseline between Week 5 and Week 24 was notably greater in the propranolol 3 mg/kg/day 6 months arm than in the placebo arm (73.0%, 73 patients, versus 5.5%, 3 patients, nominal $p < 0.0001$), based on central assessment of the 3-point scale in the ITT population.

There was consistency as regards nominal statistical significance across centralised, investigator, and parent/guardian assessments for the sustained improvement results (KM estimates) at Week 5 and Week 24 for the propranolol 3 mg/kg/day 6 months and placebo groups, based on the 3-point scale. The KM estimates for the three assessment methods, respectively, for propranolol 3 mg/kg/day 6 months versus placebo, respectively, at Week 5 were 72.7% (72 patients) versus 5.4% (3 patients), 70.9% (68 patients) versus 20.1% (10 patients) and 67.4% (64 patients) versus 19.9% (10 patients), and the KM estimates for the corresponding results at Week 24 were 79.5% (77 patients) versus 9.0% (3 patients), 82.5% (76 patients) versus 32.4% (12 patients), and 85.6% (76 patients) versus 45.0% (14 patients). The results for the KM estimates over the course of the study were nominally significant ($p < 0.0001$) for each of the three assessment methods. However, it is noted that the absolute difference between the two treatment arms for the endpoint at both Week 5 and Week 24 is notably different for the investigator and parent/guardian assessments compared with the centralised assessment, with improvement being assessed more conservatively both by investigators and parents/guardians than by centralised readers.

With respect to treatment-emergent IH complications reported in the pivotal study in the ITT population in the placebo and 3 mg/kg/day 6 months arms: treatment-emergent IH functional impairment was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment, and no patients in the active 3 mg/kg/day 6 months arm; treatment-emergent IH ulceration was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment due to inefficacy, and in 4 patients in the active 3 mg/kg/day 6 months arm (2 patients resolved while on treatment, 2 led to premature withdrawal from treatment due to inefficacy); and treatment-emergent IH bleeding/haemorrhaging was reported in 1 patient in the placebo arm resulting in premature withdrawal from treatment due to inefficacy, and 1 patient in the active 3 mg/kg/day 6 months arm that resolved while on treatment. Overall, IH complications in the pivotal study were infrequent and confirm that the IHs in this study were low-risk.

There are no confirmatory data in the submission demonstrating that propranolol 3 mg/kg/day 6 months can satisfactorily maintain efficacy following cessation of therapy. The submission included preliminary data from the pivotal study on patients who entered a 72 week open-label extension phase after completing the 24 week double-blind treatment period. Of the patients in the 3 mg/kg/day 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at Week 48 (based on centralised assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The preliminary results showed that complete/nearly complete resolution at Week 24 can be maintained through to Week 48 in patients in the propranolol 3 mg/kg/day arm (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution actually increased from Week 24 to Week 48 in the placebo arm (3.6%, 2/55 to 31.6%, 6/19). The preliminary data also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment, but before Week 48, compared with 5.3% (1/19) of patients in the placebo arm.

The efficacy data relating to treatment of IH with propranolol from the CUP are entirely observational, while the efficacy data from the sponsor's review of the scientific literature are primarily observational. The data from these two sources suggest that treatment with propranolol can improve IH in children treated with propranolol.

First round assessment of risks

There is a notably increased risk of AEs associated with propranolol compared with placebo. Some of these risks, while occurring infrequently, are particularly clinically significant (bronchospasm, hypotension, bradycardia, hypoglycaemia, and AV conduction disorders). The risks of treatment with propranolol can be mitigated by careful patient selection based

on history (including family history) and clinical examination undertaken prior to treatment, careful monitoring of HR, BP and possibly ECG over at least the first 4 h following the initial dose (Day 0) and following dose increase in the titration period (Day 7 and Day 14), and prompt recognition of AEs occurring while on treatment followed by permanent treatment discontinuation, temporary treatment discontinuation and/or symptomatic treatment as appropriate.

The risks of propranolol in adults are well known as the drug has been in clinical use for at least the last 40 years. While the drug has been used less extensively in children than in adults, there is no reason to expect that the safety profile will differ in the two populations. Overall, the risks of treatment observed in infants were consistent with the known safety profile of propranolol and generated no new safety signals.

The most clinically important identified risks with propranolol in infants include bronchospasm and bronchial hyper-reactivity reactions, bradycardia, intensification of AV block, hypotension, and hypoglycaemia including related seizures. In order to mitigate the risks of propranolol in infants the proposed Hemangiol PI recommends that treatment of infants with HI should be initiated by physician's with expertise in treatment of the condition, and in a controlled setting having facilities to manage AEs requiring urgent treatment should they arise. This is considered to be a prudent recommendation, and should apply not only to the day of initiation of treatment, but also to the days of dose increase in the titration period (that is, Day 7 and Day 14).

The most frequently reported important identified risks in the safety population were bronchospasm and bronchial hyper-reactivity. These risks were reported in 20.3% (86/424) of propranolol treated patients in the safety population. Of the 86 patients experiencing this bronchial reactions, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%) had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 2.4% (16/660) patients experience these reactions.

The important identified risk of hypotension (TEAE) was reported in 1.2% (5/424) of propranolol treated patients in the safety population (all considered by the investigator to be possibly related to treatment). In the pivotal study, BP values below the normal range were frequently observed in the active treatment arms and in the placebo arm and reductions in DBP were reported more commonly than reductions in SPB. In the pivotal study, almost all very low SBP/DBP PCSVs (< 50/30 mmHg) occurred during the titration period, and were low DBP rather than low SBP values. Over Day 7-1 h to Day 14-4 h of the titration period, the proportion of patients in the pivotal study with very low PCSVs SBP/DBP was similar in the grouped 3 mg/kg/day and placebo regimens (14.4%, 29/201, 52 events versus 14.5% 8/55, 12 events, respectively), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200; 20 events). The proportion of patients with very low PCSVs SBP/DBP decreased after the titration period in each of the treatment arms. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of bradycardia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the safety population. In the safety population, both cases were from the pivotal study and both resulted in permanent treatment discontinuation. In the pivotal study, low HR PCSVs (< 60 bpm) occurred infrequently in all treatment arms with the rates being 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of hypoglycaemia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the pooled safety population. In the pooled safety population, both events (2.5 mmol/L and 2.9 mmol/L, detected by pin-prick) occurred in the titration period and both events resolved spontaneously. One of the events was preceded by 2 to 3

days of gastroenteritis (vomiting, diarrhoea, poor feeding), but propranolol dosing was not stopped. Routine blood biochemistry during the treatment period (venous blood) revealed 2 patients with critical blood glucose values (< 2.6 mmol/L) during the titration period, with levels returning to normal while on propranolol, and 2 patients with isolated critical values at Week 24 (1, 0.4%, in the all pooled placebo group [n = 256] and 1, 0.2%, in the all propranolol group [n = 424] of the pooled safety population). In the CUP, hypoglycaemia was reported in 0.6% (4/660) of patients.

The important identified risk of intensification of AV block (TEAE) was reported in 1 (0.2%) of 424 propranolol treated patients. This event occurred almost immediately after the first dose (0.5 mg/kg) of propranolol and was considered by the sponsor to be possibly related to treatment, although there is some evidence that the event might have been related to a pre-existing cardiac disorder. In the CUP, complete AV block associated with acute heart failure resulting in deaths occurred in 1 (0.15%) of 660 patients. The events were not considered by the sponsor to be related to the study drug due to the presence of confounding factors. Of note, in the pivotal study right-bundle branch block was reported in 2 propranolol treated patients as a TEAE, and QT interval prolongation[41] was reported in 3 patients as a TEAE.

There were no reports of AV block being detected by routine, repeat ECG monitoring in the clinical trial program. The sponsor proposes that routine ECG not be undertaken before initiation of treatment. The sponsor states that in the clinical development program, ECG before initiation of treatment did not identify a single condition likely to interfere with tolerability to propranolol, while echocardiography before the initiation of treatment resulted in the non-inclusion of 1 patient on the basis of a questionable intra-cardiac mass of doubtful clinical relevance.

The risk of experiencing at least one TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, TEAEs were reported in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 versus 88.8%, 199/224, respectively). In the pooled safety population, TEAEs reported in at least 10% of patients in the all propranolol group (n = 424) versus the all placebo group (n = 236) were (in descending order of frequency): nasopharyngitis (23.6% versus 15.3%); pyrexia (21.2% versus 7.2%); diarrhoea (18.9% versus 3.4%); teething (15.3% versus 9.3%); cough (11.8% versus 7.2%); vomiting (10.6% versus 3.4%); and URTI (10.1% versus 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day 6 months arm (n = 101) versus the placebo arm (n = 55) were (in descending order of frequency): nasopharyngitis (33.7% versus 18.2%); diarrhoea (27.7% versus 7.3%); pyrexia (26.7% versus 9.1%); teething (20.8% versus 10.9%); bronchitis (16.8% versus 1.8%); URTI (13.9% versus 7.3%); vomiting (12.9% versus 5.5%); cough (11.9% versus 7.3%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); bronchiolitis (8.9% versus 5.5%); dermatitis diaper (8.9% versus 3.6%); toothache (8.9% versus 3.6%); conjunctivitis (7.9% versus 3.6%); vaccination complication (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); middle insomnia (5.0% versus 5.5%); nightmare (5.0% versus 1.8%); and rash (5.0% versus 1.8%).

In the pivotal study, clinically significant TEAEs defined as occurring in least 2% of patients in the 3 mg/kg/day 6 months arm (n = 101) and with at least a 3 fold higher incidence than in the placebo arm (n = 55) were: diarrhoea (27.7% versus 7.3%); bronchitis (16.8% versus 1.8%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); sleep disorder (6.9% versus 1.8%); ear infection (4.0% versus 0%); pharyngitis (3.0% versus 0%);

[41] The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.

viral infection (3.0% versus 0%); GORD (3.0% versus 0%); and AST increased (3.0% versus 0%). In the pivotal study, the majority of TEAEs in the treatment arms were reported to be mild or moderate in intensity, to have occurred before or at Week 12, and to have resolved by Week 24.

The risk of experiencing a treatment related TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, the percentage of patients with a least one treatment related TEAE in the all placebo group was 36.3% (154/424) compared with 14.8% (35/236) in the all placebo group. In the pivotal study, 34.7% (5/101) of patients in the 3 mg/kg/day 6 months arm experienced at least one TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day arm (n=101) and/or the placebo arm (n=55) were: peripheral coldness (8.9% versus 0%); diarrhoea (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); nightmare (5.0% versus 1.8%); middle insomnia (4.0% versus 5.5%,); vomiting (3.0%, versus 1.8%); AST increased (3.0% versus 0%); insomnia (3.0% versus 5.5%); rash (2.0% versus 0%); blood potassium increased (2.0% versus 0%), and frequent bowel motions (1.0% versus 3.6%). Only three of these events (middle insomnia, insomnia, frequent bowel motions) occurred more commonly in the placebo arm than in the propranolol 3 mg/mg/kg/day 6 months arm.

There were no deaths reported in the pooled safety population. However, there was 1 death reported in a propranolol treated patient in the CUP due to complete AV block and acute cardiac failure (mentioned above). In the pivotal study, the risk of experiencing a SAE was similar in the propranolol 3 mg/kg/day 6 months and placebo arms (5.9%, 6/101, 7 events versus 5.5%, 3/55, 3 events, respectively). Of the total number of SAEs reported in the pivotal study (33 events), 26 events occurred in 401 patients while on propranolol (0.06 events per patient), and 7 events occurred in 236 while on placebo (0.03 events per patient).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1 of condition aggravated in 1 patient in the placebo arm; 1 of AV block second degree (Mobitz I type) in the active treatment phase in the 1 mg/kg/day 6 months arm; 1 of obstructive bronchitis in the active treatment phase in the 3 mg/kg/day 3 months arm; 1 of condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day 3 months arm; and 1 of bradycardia in the active treatment phase in the 3 mg/kg/day 3 months arm. The only one of the events not categorised as a sudden unexpected serious adverse reaction (SUSAR) was bradycardia. Preliminary data from the post-Week 24 extension to the pivotal study raises no additional concerns relating to SAEs.

Permanent treatment discontinuation due to TEAEs occurred more commonly in patients treated with placebo than patients treated with propranolol. In the pivotal study, permanent treatment discontinuations due to TEAEs were reported in 10.9% (6/55) of patients in the placebo arm and 4.0% (16/401) of patients in the combined propranolol arms. In the pooled safety population, 4.7% (11/236) of patients in the all placebo group had at least one TEAE resulting in permanent treatment discontinuation compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent treatment discontinuation in ≥ 2 patients in the pooled safety population all occurred in the all placebo group (n = 236) and were condition aggravated (3, 1.3%), drug ineffective (2, 0.8%) and bronchiolitis (2, 0.8%). Temporary treatment discontinuations occurred in 63 patients in the pooled safety population, and the dose of propranolol was reduced in 4 patients in the clinical trial program.

There were no data from the clinical studies of the risks of propranolol in infants with high-risk IH, but the CUP included patients with high-risk IH. There were no data in the clinical studies on the risks of concomitant use of propranolol and other drugs. Therefore, all the known risks of interactions between the propranolol and other drug should be considered to apply to the use of the drug for the treatment of infants with IH. There were no data on the treatment of infants with IH with concomitant hepatic, renal, cardiac and/or respiratory

disease. Therefore, it is considered that all infants with IH with these concomitant conditions should not be treated with propranolol.

First round assessment of benefit-risk balance

No assessment of the benefit-risk balance of propranolol at the proposed dose for the proposed indication can be made due to the absence of pivotal data satisfactorily establishing the benefits of the drug compared with placebo.

First Round Recommendation Regarding Authorisation

It is recommended that the submission to register Hemangiol for the treatment of proliferating infantile hemangioma requiring systemic therapy be **rejected**. The reasons for this recommendation are as follows:

1. In the pivotal study, the marked benefit of treatment with propranolol 3 mg/kg/day 6 months compared with placebo for the primary efficacy endpoint of complete/nearly complete resolution of IH at Week 24, based on blinded central assessment of photographs by 2 readers, was not confirmed by blinded on-site assessment of this endpoint by investigators. The difference in outcome between the two assessment methods is considered to be important, and the results of the on-site investigator assessment by physicians experienced in the management of IH can not be dismissed. The inconsistency between the results for complete/nearly complete resolution of IH at Week 24 for the two assessment methods is considered to raise uncertainty about the true effect of propranolol compared with placebo for this outcome. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day for 6 months results in clinically significant complete/nearly complete resolution of IH at Week 24 compared with placebo.
2. In the pivotal study, there are data suggesting that propranolol 3 mg/kg/day 6 months might improve IH outcome at Week 24 compared with placebo. However, all evidence suggesting that the proposed dose provides a treatment benefit relating to improvement at Week 24 for the proposed indication is exploratory. The pivotal study was not designed to investigate improvement in outcome in IH between baseline and Week 24, and p values for all secondary efficacy endpoints up to and including Week 24 were nominal rather than confirmatory.
3. There are no pivotal data indicating that treatment benefits observed at Week 24 can be maintained following cessation of treatment. The available data suggesting that this might be the case are preliminary and considered to be exploratory.

There is no information on spontaneous regression of the target IH in patients in the pivotal study who prematurely withdrew from the study due to 'treatment inefficacy' (32/55, 58.2%). If a substantial number of these patients spontaneously regress over time, then this might have implications for the assessment of the benefit-risk balance of propranolol, even it could be established that improvement occurred significantly earlier with treatment than with placebo. This is considered to be particularly important given that the patients in the pivotal study had low-risk IHs.

Clinical Questions

The following questions regarding clinical data were raised in the TGA consolidated request for information:

Pharmacokinetics

1. For Study V00400 SB 1 01 2A, please confirm that the point estimates and 90% confidence intervals (CIs) provided in the Final Bioanalytical Report ([dossier] table 10) for the Cmax, AUC_{last}, and $AUC_{0-\infty}$ were derived from the geometric mean ratios (solution 80 mg/tablet 70.18 mg) summarised in the CSR ([dossier] tables 14.2.3-1 and 14.2.3-2). If this is confirmed, please explain why dose normalised 80 mg geometric means were not used to calculate the point estimates for Cmax, AUC_{last}, and $AUC_{0-\infty}$, and provide point estimates (solution/tablet) based on the dose normalised geometric means for the parameters. Why were the bioequivalence data not included in the body of the CSR?
2. Please justify why the propranolol oral solution formulation proposed for registration in Australia was not used in Study V00400 SB 1 01 2A.
3. Please supply a justification addressing the relevant clinical issues relating to the in vivo PK of propranolol in humans for not comparing the oral solution used in Study V00400 SB 1 01 2A with an Australian sourced propranolol 40 mg tablet rather than Avlocardyl 40 mg tablets.

Efficacy

1. In the pivotal study, was any attempt made to validate the photographic criteria used to define complete or nearly complete resolution of IH at Week 24 against the actual physical appearance of the lesion as assessed by clinical examination undertaken by physicians experienced in the assessment and management of IH?
2. Please provide the number of patients with complete resolution and the number of patients with nearly complete resolution contributing to the total number of patients with complete/nearly complete resolution for the primary efficacy endpoint analysis in the pivotal study (that is, 61 patients on propranolol 3 mg/kg/day 6 months, 2 patients on placebo).
3. The inclusion criteria for the pivotal study included a proliferating IH (target hemangioma) 'requiring systemic therapy'. Were investigators instructed to document their reasons for considering that an individual patient's IH required systemic therapy? If so, what were these reasons?
4. Does the sponsor have any information on the outcome of the IHs (for example, spontaneous regression) in the patients in the placebo arm in the pivotal study who withdrew prematurely due to lack of efficacy (32/55; 58.2%)? If not, does the sponsor intend to obtain this information and, if so, over what time-period will such information be collected?
5. In the pivotal study (CSR) is stated that the centralised readers evaluated the overall quality of the photographs for each combined image evaluation on a three-level scale: unevaluable; poor; good. What was the outcome of this quality assessment?
6. Please provide an explanation why three of the four 'Independent advisory board' members were study investigators, and therefore not independent?
7. Were the independent observers assessed for red-green colour blindness?
8. How was the IH deep component (non-visible) assessed for response?
9. How did the independent observers determine a change in: deep component, skin thickening, tenseness and soft tissue swelling from photographs?
10. Why was the glucose level of 40 mg/dL (2.2 mmol/L) used as the cut off to describe hypoglycaemia and not 2.6 mmol/L as is standard in clinical practice?

11. What are the results of the Kappa statistic for intra- and inter-observer error as described in the method section?

Safety

1. Please provide a tabulated summary of patients in the pooled safety population with temporary treatment discontinuations by treatment group (that is, all placebo [n = 236], all 1 mg/kg/day [n = 200], all 3 mg/kg/day [n = 224], and all propranolol [n = 424]). The table should summarise the data in the same manner as the data for TEAEs resulting in permanent treatment discontinuation summarised in the ISS/SCS ([dossier] table 23). In addition, please provide information on the mean duration (and range) of the total temporary treatment discontinuations for each of the treatment groups.
2. Please provide the proportion of patients in the pivotal study (201) and the pooled safety population with HR values less than 80 bmp in each treatment arm during the course of treatment, and indicate the number (and percentage) of these events occurring during and after the titration period. The proposed Hemangiol PI recommends that specialist advice be sought for patients with bradycardia (HR < 80 bpm). Please explain why the cutoff figure of 80 bpm was chosen as the point for intervention.
3. Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population in the first 4 h following the first dose (Day 0) and following dose increase in the titration period (Day 7, and Day 14).
4. Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population during the course of the study.
5. Were any patients permanently or temporarily discontinued from treatment due to abnormalities detected by routine ECG monitoring in the clinical development program. If so, please provide information on these patients
6. In the clinical development program, how many patients had routine echocardiography undertaken before treatment with propranolol was initiated and confirm that only one patient was excluded from treatment because of detected abnormalities.
7. In the ISS/SCS, patients with at least one TEAE occurring on the days of dose increase are presented by pooled dose of Hemangiol or placebo for Day 1 in [the dossier] table 2.7.4.2.29b ([dossier] section 5.3.5.3 – Vol. 1), for Day 7 in table 2.7.4.2.30b (section 5.3.5.3 – Vol. 1) and for Day 14 in table 2.7.4.2.31b (section 5.3.5.3 – Vol. 1). The summary states that on Day 1, Day 7 and Day 14, no TEAEs were experienced in the pooled placebo group. However, this statement appears to be inconsistent with the tables referred to in the [study] summary which suggest that 4, 2, and 5 patients in the placebo group experienced AEs on Day 0, Day 7, and Day 14, respectively. Please comment on this apparent discrepancy.
8. Please describe the types of vaccination reaction for both the treatment and placebo groups, and explain why the treatment group had such a high rate of reported AEs?
9. Did any of the subjects treated with propranolol who did not achieve a treatment response have their lesions biopsied to confirm the diagnosis? Other conditions such as hemangioendothelioma may visually appear like an IH but are frequently propranolol insensitive and many require chemotherapy, or other treatments, to achieve resolution.
10. What were the diagnoses for [3 patients with alkaline phosphatase of 4843 international units (IU)/L, 2207 IU/L and 937 IU/L, respectively]?
11. What was the cause of the two episodes of cytolytic hepatitis in a patient?

12. What was the cause of the persistent thrombocytosis and neutropenia seen in a patient? Why was this not considered an AE?
13. How many premature infants were in the treatment and placebo groups? Did all premature infants that received propranolol commence after 5 weeks of age?

Second Round Evaluation of Clinical Data Submitted in Response to Questions

The evaluator's assessment of the sponsor responses are shown below. Full details of the sponsor responses are shown in Attachment 2 (CER extract).

Pharmacokinetics

Question 1

The sponsor's response is satisfactory. The dossier table 14.2.3-3 in the report for study V00400 SB 1 01 2A has been reviewed. The table provides dose normalised (80 mg) test [solution]/reference [tablet] results for the Cmax and the $AUC_{0-\infty}$ for each of the 12 individual subjects with evaluable data, and mean values for each of these two parameters. The mean Cmax ratio (solution/tablet) was 1.22 (range: 0.32, 3.98), indicating that the mean Cmax was 22% higher for the solution compared with the tablet, and the mean $AUC_{0-\infty}$ ratio (solution/table) was 1.20 (range: 0.5, 3.28), indicating that the mean $AUC_{0-\infty}$ was 20% higher for the solution compared with the tablet. No 90% CI was provided for either of the two parameters, but it can be reasonably inferred from the point estimates that the upper bound of the 90% CI for both parameters will be greater than 1.25 and that the 90% CIs will not be completely enclosed within the standard bioequivalence limits of 0.80-1.25.

Question 2

It is recommended that the Module 3 (quality) evaluator comment on the sponsor's response. A section in the dossier relates to the pharmaceutical development of the product and is headed 'Initial Risk Assessment of Drug Substance Attributes'. The section notes that, according to the BCS, propranolol hydrochloride is a class 1 drug substance (high solubility, high permeability). The section also includes an assessment of the effect of pH on the solubility of the propranolol hydrochloride solution.

Question 3

The sponsor's response is satisfactory. However, it is recommended that comment on the response be obtained from the Module 3 [quality] evaluator.

Efficacy

Question 1

The sponsor's detailed response to the question has been provided in full (see Attachment 2, CER extract) as the efficacy of Hemangiol for the proposed indication hinges on the interpretation of the data summarised in the response.

The sponsor's response indicates that the photographic criteria used to define complete or nearly complete resolution of IH at Week 24 were not validated by comparison with the actual physical appearance of the lesion as assessed by clinical examination undertaken by physicians experienced in the assessment and management of IH. Therefore, the centralised (photograph) assessment of outcome should be considered to be a non-validated surrogate measure of the outcome of interest, which is considered to be complete/nearly complete resolution of the IH following treatment assessed by 'in vivo' clinical examination.

There is no doubt that the results of the primary efficacy endpoint analysis of complete/nearly complete resolution of target IH at Week 24, based on centralised comparative assessment of the Baseline and Week 24 photographs, are statistically robust. However, the sponsor claims that the results are also clinically robust based on the endpoint of change in lesion as assessed photographically by two experienced physicians. The sponsor justifies the use of the photographs to assess clinical change in IH following treatment on the basis that interpretation can be centralised and standardised resulting in minimisation of bias. However, it is considered that assessment of change in the IH following treatment based on physical examination of the lesion by experienced physicians is a more clinically relevant method of assessing progress than photographic evidence.

The primary endpoint analysis showed that the complete/nearly complete resolution rate at Week 24 of the target IH in the ITT data set was statistically significantly higher in the propranolol group (3 mg/kg/day for 6 months) than in the placebo group: 60.4% (61/101) versus 3.6% (2/55), respectively; $p < 0.0001$. The results of the analyses of the primary outcome endpoint in the PP data set and the sensitivity analyses in the ITT data set (planned and unplanned) also showed that the complete/nearly complete response rates in the propranolol group were statistically significantly higher than in the placebo group. The placebo response rates in the planned and unplanned sensitivity analyses were markedly higher than the placebo response rates in the ITT and PP sets, while the propranolol response rates remained consistent in the four analyses. This appears to be a function of the methods used in sensitivity analyses, which resulted in inflating the placebo response rate, given that nearly all patients in the placebo group in the primary analysis were non-responders. In addition to the PP and sensitivity analyses, the subgroup analyses of the primary endpoint also support the primary efficacy analysis.

The results of the primary analysis based on centralised assessment of photographic progression of the target IH at Week 24 are inconsistent with the protocol specified secondary analysis based on investigator assessment of treatment outcome. In the pre-specified investigator assessment, the complete/nearly complete resolution rate at Week 24 of the target IH was 10.5% (2/19) compared with 26.7% (24/90) in the propranolol group, $p = 0.4419$. The sponsor considers that the reason for this discrepancy 'is most likely attributable to subjectivity in the definition of complete/near complete resolution which may be influenced by differences in training, standard treatment used in the centres and expectations (of Investigators and parents)'. The sponsor rejects the possibility that the difference is due to bias in the centralised photographic assessment and refers to the evidence supporting the validity of the assessment procedure. However, review of the evidence provided by the sponsor is considered to show that centralised assessment has 'internal validity', but no evidence has been provided that the method accurately reflects the progression of IH detectable by physical examination by experienced physicians (that is, 'external validity').

The investigator assessment of complete/nearly complete resolution was undertaken on a different patient population from that used for the centralised photographic assessment. The sponsor considered that the investigator assessment resulted in an overestimation of the Week 24 complete/nearly complete success rate in the placebo group due to the large number of patients in this group discontinuing for lack of efficacy being classified as 'missing data' rather than as 'treatment failures'. Consequently, the sponsor undertook a post hoc analysis where the investigator assessment at Week 24 was transformed into a binary outcome using the same approach to categorisation of patients as the primary analysis. In this post hoc analysis, patients were considered to be 'treatment failures' if the investigator assessment at Week 24 was not a 'complete or nearly complete response', if the patient discontinued treatment prematurely, or if the patient took additional treatment for IH before Week 24. These data were then analysed using the same statistical methods as the primary analysis.

The results of the post hoc analysis showed that there was a statistically significant difference in the success rate between the placebo and propranolol groups at Week 24 (3.6% [2/55] versus 22.8% [23/101; p = 0.004). In the post hoc analysis, while the complete/nearly complete resolution success rate in the placebo group was identical to that in the primary efficacy analysis (3.6%), the success rate in the propranolol 3 mg/kg/day group remained strikingly lower than in the primary analysis (22.8% versus 60.4%, respectively).

The sponsor undertook a comparison between the patients who had convergent or divergent treatment outcomes (success versus failure) at Week 24 for the primary centralised assessment and post hoc investigator assessment. This comparison found that, while both assessments were fully convergent for the outcome of 'treatment failure' in both the placebo and propranolol groups, the assessments were markedly divergent for the outcome of 'treatment success' in the propranolol group. The sponsor states that the results suggest 'that the centralised and Investigators' assessment of treatment failure was consistent, but that the Investigators applied a more stringent and subjective interpretation of treatment success compared to the centralised assessment. It was to avoid such subjectivity that the centralised assessment was chosen as the primary efficacy outcome'. However, another reason might be that centralised assessment of IH progression based on photographic changes is not a particularly reliable measure of progression assessed by physical examination by experienced physicians. Furthermore, no data were presented establishing that assessments were subjectively different among investigators. Therefore, the sponsor's contention that the investigators applied a more stringent and subjective interpretation of treatment success compared with the centralised assessors is considered to be speculative.

The results of the KM assessment of time to first improvement in IH evolution on a qualitative 3 point scale (improvement, worsening, or stabilisation) showed that analyses for the propranolol group converged at Week 24 for centralised, investigator on-site and parent-on-site assessments (KM rates: 79.5%, 82.5% and 85.6%, respectively). However, analyses were non-convergent for the placebo group at Week 24 with the KM rates being markedly lower for centralised assessment compared with both investigator on-site and patient on-site assessments (KM rates: 9.0%, 32.4%, and 45.0%, respectively). In each of the three assessment groups, the difference between placebo and propranolol were statistically significant.

The results of the post hoc KM assessment of time to first worsening (improvement, worsening, or stabilisation) showed that at Week 24 both centralised and investigator on-site assessments converged, and showed notably more patients with IH worsening in the placebo group (KM rate: 69.1% and 75.9%, respectively) than in the propranolol group (KM rates: 19.9% versus 26.3%, respectively).

In conclusion, it is considered that the marked inconsistency in the complete/nearly complete resolution rate in the propranolol group between the primary centralised assessment (60.4% [61/101]) and both the protocol specified investigator's assessment (26.7% [24/101]), and the post hoc investigator's assessment (22.8% [23/101]) in the pivotal study raises doubts about the efficacy of propranolol for the proposed usage. While propranolol might be an effective treatment for IH it is considered that the pivotal study has not unequivocally demonstrated that this is the case.

Questions 2-11

The sponsor's responses are satisfactory (see CER extract, Attachment 2).

Safety

Question 1

The sponsor provided the requested tables. The sponsor stated that a total of 53 patients had a temporary treatment discontinuation due to TEAEs. This number is incorrect as it refers to the total number of patients in the combined propranolol groups (that is, excludes patients in the all placebo group). The total number of patients with a temporary treatment discontinuation due to TEAEs was 63 (10 [4.2%] in the all placebo group and 53 [12.5%]) in the all propranolol group.

Temporary treatment discontinuations due to TEAEs occurred notably more commonly in the all propranolol 3 mg/kg/day group than in the all placebo group (15.2% [34/244] versus 4.2% [10/236], respectively). TEAEs resulting in temporary treatment discontinuation reported in ≥ 1% of patients in the all placebo or all propranolol 3 mg/kg/day groups, and in descending order of frequency in the propranolol group versus the placebo group were: bronchitis (3.1% versus 0.8%); gastroenteritis (3.1% versus 0.4%); bronchiolitis (2.2% versus 2.1%); vomiting (2.2% versus 0%); and pyrexia (1.3% versus 0%). The only TEAE resulting in temporary treatment discontinuation reported more frequently in the all placebo group than in the all propranolol 3 mg/kg/day group was febrile infection (0.4% versus 0%, respectively).

Question 2

The sponsor's response is satisfactory. The response included a set of 4 tables that included data from the total safety population in addition to data from the pivotal study (201). However, the headings of two tables appear to be associated with the wrong data sets. In any event, the data provided for the pivotal study (201) for the safety included above indicate that by Month 6, 14.9% of patients in the propranolol 3 mg/kg/day group had experienced at least one episode of bradycardia (HR < 80 bpm) compared with 5.5% of patients in the placebo group. In addition, bradycardia occurred notably more commonly in the 3 mg/kg/day group during up-titration than in the placebo group. There was also a dose response relationship between bradycardia and propranolol. In the pooled safety population, the proportion of patients experiencing at least one episode of bradycardia (HR < 80 bpm) in the treatment period in the placebo, all propranolol 1 mg/kg/day, and all propranolol 3 mg/kg/day groups was 2.5% (6/236), 6.5% (13/200), and 14.3% (32/224), respectively. The pattern for bradycardia in the pooled safety population was similar to that observed in the pivotal study (201). Overall, the results indicate that bradycardia (HR < 80 bpm) occurred relatively frequently with the propranolol 3 mg/kg/day treatment region and notably more commonly than with placebo.

Questions 3-13

The sponsor's responses are satisfactory (see CER extract, Attachment 2).

Second Round Benefit-Risk Assessment

Second round assessment of benefits

Following evaluation of the sponsor's response to questions, the second round assessment of the benefits of Hemangiol remains largely unchanged from the first round assessment. While it is possible that Hemangiol might provide a benefit to infants aged from 30 to 150 days with proliferating IH requiring systemic therapy, it is considered that this has not been unequivocally demonstrated in the pivotal study (Study V00400 SB 2 01).

In the pivotal study, the proportion of infants aged from 30 to 150 days achieving complete/nearly complete resolution of proliferating IH requiring systemic therapy at Week 24 was markedly higher in the propranolol 3 mg/kg/day x 6 months arm than in the placebo arm, based on centralised (blinded) reading of patient photographs in the ITT data set (60.4%, 61/101, versus 3.6%, 2/55, respectively, $p < 0.0001$). The absolute difference between the active and placebo treatment arms (56.8%) indicates that approximately 2 patients need to be treated with propranolol 3 mg/kg/day for 6 months arm in order for 1 of them to show a complete or nearly complete resolution in their IH at Week 24 based on photographic data (that is, number needed to treat [NNT] = 2). However, the results for the primary efficacy analysis for complete/nearly complete resolution of IH at Week 24 were strikingly inconsistent with the results for this outcome based on investigator on-site assessment in the propranolol 3 mg/kg/day for 6 months and placebo arms (26.7%, 24/90, versus 10.5%, 2/19, respectively, $p = 0.4419$).

In the response to the TGA consolidated request for information the sponsor argues that the discrepancy between the results of the primary and secondary assessments of complete/nearly complete resolution of the target IH at Week 24 was most likely attributable to subjective differences among investigators in the interpretation of complete/nearly complete resolution. Furthermore, the sponsor considered that the differences in interpretation of the outcome 'may be influenced by differences in training, standard treatment used in the centres, and expectations (On investigator's and parents)'. The sponsor stated that it adopted centralised assessment of outcome based on standardised interpretation of photographic evidence by trained observers because of the potential for subjective interpretation resulting from clinical determination of complete/nearly complete resolution by individual investigators.

The sponsor rejects the possibility that the difference in outcome between the primary and secondary analyses was due to bias in the centralised assessment (photographs) procedure. However, no validation of treatment outcomes based on the centralised assessment (photographs) procedure with treatment outcomes based on clinical examination undertaken by experienced physicians was undertaken. The sponsor considers that such validation is unnecessary given the methods used to develop and apply the centralised assessment (photographs) procedure and the robustness of the statistical analyses of the outcome (that is, strongly positive results favouring propranolol compared with placebo in the primary analysis in the ITT data supported by analysis in the PP data set and two sensitivity analyses [one planned, one unplanned]). However, it is considered that, while the sponsor has demonstrated the 'internal validity' of the centralised assessment (photographs) procedure, no evidence has been provided demonstrating that the procedure reliably predicts treatment outcomes determined from clinical examination by experienced physicians (that is, 'external validity'). It is considered that the results of physical assessment of treatment outcome in children with progressive IH by experienced physicians should be the 'gold standard' against which all surrogate assessments, such as centralised assessment based on photographic appearance of the lesion, should be validated.

The sponsor also argues that the methodology used to classify patients in the placebo group who discontinued due to lack of efficacy in the pre-specified secondary analysis of investigator assessed complete/nearly complete resolution resulted in an overestimation of success at Week 24 in this group. The 'overestimation' was due to the large number of patients in the placebo group who discontinued because of lack of efficacy being classified as 'missing data' rather than as 'treatment failures'. In order to address this matter, the response to the TGA request for information included a post hoc analysis in which the Week 24 investigator assessment was transformed into a binary outcome (treatment success versus treatment failure) with missing data, premature discontinuations, and additional IH treatments being handled as treatment failures (that is, same approach used for the primary analysis). In this post hoc analysis, complete/nearly complete resolution at Week 24 investigator assessment (treatment success) in the propranolol 3 mg/kg/day for 6 months

arm was statistically significantly greater than in the placebo arm (22.8% [23/101] versus 3.6% [23/101], respectively, p = 0.004). The complete/nearly complete resolution rate in the placebo arm in the post hoc analysis of investigator assessment was identical to the corresponding rate in the placebo arm in the primary analysis of centralised (photography) assessment (3.6%), but the rates for this outcome in the propranolol 3 mg/kg/day x 6 months arms remained strikingly discordant between the primary and post hoc analyses (60.4% versus 22.8%, respectively).

The sponsor stated that the result of the post hoc analysis suggest 'that the centralised and Investigators' assessment of treatment failure was consistent, but that the Investigators applied a more stringent and subjective interpretation of treatment success compared to the centralised assessment. It was to avoid such subjectivity that the centralised assessment was chosen as the primary efficacy outcome'. However, the difference between assessment methods might be that centralised assessment of IH progression based on photographic changes is not a particularly reliable measure of progression compared with physical examination by experienced physicians. Furthermore, no data were presented establishing that assessments were subjectively different among investigators. Therefore, the sponsor's contention that the investigators applied a more stringent and subjective interpretation of treatment success compared with the centralised assessors is considered to be speculative.

The marked difference between the complete/nearly complete resolution rate at Week 24 observed following treatment with the propranolol 3 mg/kg/day for 6 months regimen between the primary centralised (photography) assessment (60.4% [61/101]) and the pre-specified investigator (26.7% [24/101]) and post hoc investigator (22.8% [23/101]) assessments cannot be discounted. It is considered that the striking lack of consistency between the centralised (photography) and investigator on-site assessments of complete/nearly complete resolution of progressive IH at Week 24 following propranolol 3 mg/kg/day for 6 months in the pivotal study raises doubts about the benefits of this treatment for this condition.

The efficacy endpoints in the pivotal study relating to qualitative improvement in the appearance of the IH based on a 3 point scale (improvement, worsening or stabilisation) are considered to be exploratory. The pre-specified KM analysis of time to first sustained improvement after which there was no worsening at each time point through to and including Week 24 showed that the proportion of patients achieving this endpoint (KM estimates) was notably higher (nominal p < 0.001) in the propranolol 3 mg/kg/day for 6 months arm than in the placebo arm for the centralised, investigator on-site and parent on-site assessments. There was convergence between the three assessment methods for the propranolol 3 mg/kg/day for 6 months arm, but not for the placebo arm where the proportion of patients achieving sustained improvement at each time point through to and including Week 24 was notably lower with the centralised assessment than with the investigator and parent on-site assessments. The post hoc survival analysis of time to first worsening from randomisation showed that time to first worsening through to Week 24 was notably shorter with placebo than with propranolol 3 mg/kg/day x 6 months arm, and that this result was convergent for the centralised and investigator on-site assessments. Overall, the qualitative improvements in IH data through to Week 24 suggest that propranolol 3 mg/kg/day for 6 months might be more effective than placebo, but these data are considered to be exploratory rather than definitive.

In the pivotal study, improvement in the surface area, maximal diameter and colour of the IH from baseline to Week 12 and Week 24 were observed in the propranolol 3 mg/kg/day for 6 months arm compared with placebo. Global improvement (yes/no) from baseline between Week 5 and Week 24 was notably greater in the propranolol 3 mg/kg/day for 6 months arm than in the placebo arm (73.0%, 73 patients, versus 5.5%, 3 patients, nominal p < 0.0001), based on central assessment in the ITT population.

With respect to treatment emergent IH complications reported in the pivotal study in the ITT population in the placebo and 3 mg/kg/day for 6 months arms: treatment emergent IH functional impairment was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment, and no patients in the active 3 mg/kg/day for 6 months arm; treatment emergent IH ulceration was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment due to inefficacy, and in 4 patients in the active 3 mg/kg/day for 6 months arm (2 patients resolved while on treatment, 2 led to premature withdrawal from treatment due to inefficacy); and treatment emergent IH bleeding/haemorrhaging was reported in 1 patient in the placebo arm resulting in premature withdrawal from treatment due to inefficacy, and 1 patient in the active 3 mg/kg/day for 6 months arm that resolved while on treatment. Overall, IH complications in the pivotal study were infrequent and confirm that the IHs in this study were low-risk.

There are no confirmatory data in the submission demonstrating that propranolol 3 mg/kg/day for 6 months can satisfactorily maintain efficacy following cessation of therapy. The submission included preliminary data from the pivotal study on patients who entered a 72 week open-label extension phase after completing the 24 week double-blind treatment period. Of the patients in the 3 mg/kg/day for 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at Week 48 (based on centralised assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The preliminary results showed that complete/nearly complete resolution at Week 24 can be maintained through to Week 48 in patients in the propranolol 3 mg/kg/day for 6 months arm (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution actually increased from Week 24 to Week 48 in the placebo arm (3.6%, 2/55 to 31.6%, 6/19). The preliminary data also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day for 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment, but before Week 48, compared with 5.3% (1/19) of patients in the placebo arm. There are no data in the submission on the spontaneous regression rate in patients in the placebo arm.

The efficacy data relating to treatment of IH with propranolol from the CUP are entirely observational, while the efficacy data from the sponsor's review of the scientific literature are primarily observational. The primarily observational data from these two sources suggest that treatment with propranolol can improve IH in children treated with propranolol.

Second round assessment of risks

Following evaluation of the sponsor's response to the TGA consolidate request for information, the second round assessment of the risks of Hemangiol remains largely unchanged from the first round assessment.

There is a notably increased risk of AEs associated with propranolol compared with placebo for the treatment of IH. Some of these risks, while occurring infrequently, are particularly clinically significant (bronchospasm, hypotension, bradycardia, hypoglycaemia, and AV conduction disorders). The risks of treatment with propranolol can be mitigated by careful patient selection based on history (including family history) and clinical examination undertaken prior to treatment, careful monitoring of HR, BP, and possibly ECG over at least the first 4 h following the initial dose and subsequent dose increases, and prompt recognition of AEs occurring while on treatment followed by permanent treatment discontinuation, temporary treatment discontinuation and/or symptomatic treatment as appropriate.

The risks of propranolol in adults are well known as the drug has been in clinical use for at least the last 40 years. While the drug has been used less extensively in children than in adults, there is no reason to expect that the safety profile will differ in the two populations.

Overall, the risks of treatment observed in infants were consistent with the known safety profile of propranolol and generated no new safety signals.

The most clinically important identified risks with propranolol in infants include bronchospasm and bronchial hyper-reactivity reactions, bradycardia, intensification of AV block, hypotension, and hypoglycaemia including related seizures. In order to mitigate the risks of propranolol in infants the proposed Hemangiol PI recommends that treatment with HI should be initiated by physician's with expertise in treatment of the condition, and in a controlled setting having facilities to manage AEs requiring urgent treatment should they arise. This is considered to be a prudent recommendation, and should apply not only to the day of initiation of treatment, but also to the days of dose increase.

The most frequently reported important identified risks in the safety population were bronchospasm and bronchial hyper-reactivity. These risks were reported in 20.3% (86/424) of propranolol treated patients in the safety population. Of the 86 patients experiencing this bronchial reactions, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%) had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 2.4% (16/660) patients experience these reactions.

The important identified risk of hypotension (TEAE) was reported in 1.2% (5/424) of propranolol treated patients in the safety population (all considered by the investigator to be possibly related to treatment). In the pivotal study, BP values below the normal range were frequently observed in the active treatment arms and in the placebo arm, and reductions in DBP were reported more commonly than reductions in SPB. In the pivotal study, almost all very low SBP/DBP potentially clinically significant values (< 50/30 mmHg) occurred during the titration period, and were low DBP values rather than low SBP values. Over Day 7-1 h to Day 14-4 h of the titration period, the proportion of patients in the pivotal study with very low potentially clinically significant SBP/DBP values was similar in the grouped 3 mg/kg/day and placebo regimens (14.4%, 29/201, 52 events versus 14.5% 8/55, 12 events, respectively), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200; 20 events). The proportion of patients with very low PCSVs SBP/DBP decreased after the titration period in each of the treatment arms. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of bradycardia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the safety population. In the safety population, both cases were from the pivotal study and both resulted in permanent treatment discontinuation. In the pivotal study, low HR potentially clinically significant values (< 60 bpm) occurred infrequently in all treatment arms with the rates being 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day for 3 months, 1 mg/day/kg for 6 months, 3 mg/kg/day for 3 months, and 3 mg/kg/day for 6 months arms, respectively. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

However, when bradycardia was defined as HR < 80 bpm, rather than < 60 bpm (the point for intervention), a notably greater proportion of subjects in the propranolol 3 mg/kg/day for 6 month arm experienced this event at least once during the pivotal study (safety population) than in the placebo arm (14.9% [15/101] versus 5.5% [3/55], respectively). Overall, in the pivotal study, at least one HR < 80 bpm event was experienced in the placebo, 1 mg/day/kg for 3 months, 1 mg/kg/day for 6 months, 3 mg/kg/day for 3 months and 3 mg/kg/day for 6 months with frequencies of 5.5%, 7.1%, 5.9%, 14.6% and 14.9%.

The important identified risk of hypoglycaemia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the pooled safety population. In the pooled safety population, both events (2.5 mmol/L and 2.9 mmol/L, detected by pin-prick) occurred in the titration period and both events resolved spontaneously. One of the events was preceded by 2 to 3 days of gastroenteritis (vomiting, diarrhoea, poor feeding), but propranolol dosing was not stopped. Routine blood biochemistry during the treatment period (venous blood) revealed 2

patients with critical blood glucose values (< 2.6 mmol/L) during the titration period, with levels returning to normal while on propranolol, and 2 patients with isolated critical values at Week 24 (1, 0.4%, in the all pooled placebo group [n = 256] and 1, 0.2%, in the all propranolol group [n = 424] of the pooled safety population). In the CUP, hypoglycaemia was reported in 0.6% (4/660) of patients.

The important identified risk of intensification of AV block (TEAE) was reported in 1 (0.2%) of 424 propranolol treated patients. This event occurred almost immediately after the first dose (0.5 mg/kg) of propranolol and was considered by the sponsor to be possibly related to treatment, although there is some evidence that the event might have been related to a pre-existing cardiac disorder. In the CUP, complete AV block associated with acute heart failure resulting in death occurred in 1 (0.15%) of 660 patients. The events were not considered by the sponsor to be related to the study drug due to the presence of confounding factors. Of note, in the pivotal study right-bundle branch block was reported in 2 propranolol treated patients as a TEAE, and QT prolongation was reported in 3 patients as a TEAE.

There were no reports of AV block being detected by routine, repeat ECG monitoring in the clinical trial program. The sponsor proposes that routine ECG not be undertaken before initiation of treatment. The sponsor states that in the clinical development program, ECG before initiation of treatment did not identify a single condition likely to interfere with tolerability to propranolol, while echocardiography before the initiation of treatment resulted in the non-inclusion of 1 patient on the basis of a questionable intra-cardiac mass of doubtful clinical relevance.

In the pivotal study, a total of 9 patients experienced one PR[42] > 160 msec event (1.8% [1/55] of patients in the placebo arm, 4.1% [51/123] of patients in the 3 mg/kg/day for 3 months arm, and 3.0% [3/101] of patients in the 3 mg/kg/day for 6 months arm]. One patient in the 1 mg/kg/day for 3 months arm experienced second degree AV block (Mobitz I type), and no patients experienced third degree AV block.

The risk of experiencing at least one TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, TEAEs were reported in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 versus 88.8%, 199/224, respectively). In the pooled safety population, TEAEs reported in at least 10% of patients in the all propranolol group (n = 424) versus the all placebo group (n = 236) were (in descending order of frequency): nasopharyngitis (23.6% versus 15.3%); pyrexia (21.2% versus 7.2%); diarrhoea (18.9% versus 3.4%); teething (15.3% versus 9.3%); cough (11.8% versus 7.2%); vomiting (10.6% versus 3.4%); and URTI (10.1% versus 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day for 6 months arm (n = 101) versus the placebo arm (n = 55) were (in descending order of frequency): nasopharyngitis (33.7% versus 18.2%); diarrhoea (27.7% versus 7.3%); pyrexia (26.7% versus 9.1%); teething (20.8% versus 10.9%); bronchitis (16.8% versus 1.8%); URTI (13.9% versus 7.3%); vomiting (12.9% versus 5.5%); cough (11.9% versus 7.3%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); bronchiolitis (8.9% versus 5.5%); dermatitis diaper (8.9% versus 3.6%); toothache (8.9% versus 3.6%); conjunctivitis (7.9% versus 3.6%); vaccination complication (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); middle insomnia (5.0% versus 5.5%); nightmare (5.0% versus 1.8%); and rash (5.0% versus 1.8%).

In the pivotal study, clinically significant TEAEs defined as occurring in least 2% of patients in the 3 mg/kg/day for 6 months arm (n = 101) and with at least a 3-fold higher incidence than in the placebo arm (n = 55) were: diarrhoea (27.7% versus 7.3%); bronchitis (16.8% versus

[42] Interval from start of the P-wave to start of the QRS complex of the ECG

1.8%); gastroenteritis (10.9% versus 3.6%); peripheral coldness (9.9% versus 1.8%); sleep disorder (6.9% versus 1.8%); ear infection (4.0% versus 0%); pharyngitis (3.0% versus 0%); viral infection (3.0% versus 0%); GORD (3.0% versus 0%); and AST increased (3.0% versus 0%). In the pivotal study, the majority of TEAEs in the treatment arms were reported to be mild or moderate in intensity, to have occurred before or at Week 12, and to have resolved by Week 24.

The risk of experiencing a treatment related TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, the percentage of patients with a least one treatment related TEAE in the all placebo group was 36.3% (154/424) compared with 14.8% (35/236) in the all placebo group. In the pivotal study, 34.7% (5/101) of patients in the 3 mg/kg/day for 6 months arm experienced at least one TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day arm (n = 101) and/or the placebo arm (n = 55) were: peripheral coldness (8.9% versus 0%); diarrhoea (7.9% versus 3.6%); sleep disorder (6.9% versus 1.8%); nightmare (5.0% versus 1.8%); middle insomnia (4.0% versus 5.5%,); vomiting (3.0%, versus 1.8%); AST increased (3.0% versus 0%); insomnia (3.0% versus 5.5%); rash (2.0% versus 0%); blood potassium increased (2.0% versus 0%), and frequent bowel motions (1.0% versus 3.6%). Only three of these events (middle insomnia, insomnia, frequent bowel motions) occurred more commonly in the placebo arm than in the propranolol 3 mg/mg/kg/day for 6 months arm.

There were no deaths reported in the pooled safety population. However, there was 1 death reported in a propranolol treated patient in the CUP due to complete AV block and acute cardiac failure (mentioned above). In the pivotal study, the risk of experiencing a SAE was similar in the propranolol 3 mg/kg/day for 6 months and placebo arms (5.9%, 6/101, 7 events versus 5.5%, 3/55, 3 events, respectively). Of the total number of SAEs reported in the pivotal study (33 events), 26 events occurred in 401 patients while on propranolol (0.06 events per patient), and 7 events occurred in 236 while on placebo (0.03 events per patient).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1 of condition aggravated in 1 patient in the placebo arm; 1 of AV block second degree (Mobitz I type) in the active treatment phase in the 1 mg/kg/day for 6 months arm; 1 of obstructive bronchitis in the active treatment phase in the 3 mg/kg/day for 3 months arm; 1 of condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day for 3 months arm; and 1 of bradycardia in the active treatment phase in the 3 mg/kg/day for 3 months arm. The only one of the events not categorised as a sudden unexpected serious adverse reaction (SUSAR) was bradycardia. Preliminary data from the post-Week 24 extension to the pivotal study raises no additional concerns relating to SAEs.

Permanent treatment discontinuation due to TEAEs occurred more commonly in patients treated with placebo than patients treated with propranolol. In the pivotal study, permanent treatment discontinuations due to TEAEs were reported in 10.9% (6/55) of patients in the placebo arm and 4.0% (16/401) of patients in the combined propranolol arms. In the pooled safety population, 4.7% (11/236) of patients in the all placebo group had at least one TEAE resulting in permanent treatment discontinuation compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent treatment discontinuation in ≥ 2 patients in the pooled safety population all occurred in the all placebo group (n = 236) and were condition aggravated (3, 1.3%), drug ineffective (2, 0.8%) and bronchiolitis (2, 0.8%).

In the pooled safety population, the risk of temporary treatment discontinuations due to TEAEs was notably higher in patients in the all 3 mg/kg/day propranolol group than in the all placebo group (15.2% [34/224]] versus 4.2% [10/236], respectively). TEAEs resulting in temporary treatment discontinuation reported in ≥ 1% of patients in the all placebo or all propranolol 3 mg/kg/day groups, and in descending order of frequency in the propranolol

group versus the placebo group were: bronchitis (3.1% versus 0.8%); gastroenteritis (3.1% versus 0.4%); bronchiolitis (2.2% versus 2.1%); vomiting (2.2% versus 0%); and pyrexia (1.3% versus 0%). The only TEAE resulting in temporary treatment discontinuation reported more frequently in the all placebo group than in the all propranolol 3 mg/kg/day group was febrile infection (0.4% versus 0%, respectively).

There were no data from the clinical studies of the risks of propranolol in infants with high-risk IH, but the CUP included patients with high-risk IH. There were no data in the clinical studies on the risks of concomitant use of propranolol and other drugs. Therefore, all the known risks of interactions between the propranolol and other drug should be considered to apply to the use of the drug for the treatment of infants with IH. There were no data on the treatment of infants with IH with concomitant hepatic, renal, cardiac and/or respiratory disease. Therefore, it is considered that all infants with IH with these concomitant conditions should not be treated with propranolol.

Second round assessment of benefit-risk balance

Following consideration of the initial submission and the sponsor's response to the first round clinical questions it is considered that the benefit-risk balance for propranolol at the proposed dose is unfavourable. The efficacy data from the pivotal study in patients aged 30 to 150 days with low-risk progressive IH requiring treatment have not unequivocally demonstrated that propranolol administered at a dose of 3 mg/kg/day results in a clinically significant benefit of complete/nearly complete resolution of IH at Week 24 compared with placebo. However, the safety data from the pivotal study have demonstrated that the risks of treatment with propranolol 3 mg/kg/day for the proposed indication are greater than the risks of placebo.

Second Round Recommendation Regarding Authorisation

Following consideration of the initial submission and the sponsor's Response to the first round clinical questions it is recommended that the application to register Hemangiol for the treatment of proliferating infantile hemangioma requiring systemic therapy **be rejected**. The reasons for this recommendation are as follows:

1. In the pivotal study, the marked benefit of treatment with propranolol 3 mg/kg/day for 6 months compared with placebo for the primary efficacy endpoint of complete/nearly complete resolution of IH at Week 24, based on blinded central assessment of photographs by 2 readers (60.4% versus 3.6%, respectively, $p < 0.0001$), was not confirmed by blinded on-site assessment of this endpoint by investigators (26.7% versus 10.5%, respectively, $p = 0.4419$). The difference in outcome between the two assessment methods is considered to be important, and the results of the on-site investigator assessment by physicians experienced in the management of IH cannot be dismissed. The inconsistency between the results for complete/nearly complete resolution of IH at Week 24 for the two assessment methods is considered to raise uncertainty about the true effect of propranolol compared with placebo for this outcome. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day for 6 months results in clinically significant complete/nearly complete resolution of IH at Week 24 compared with placebo.
2. In the pivotal study, a post hoc analysis of the investigator on-site assessment using the same methodology as that adopted for the primary efficacy endpoint showed a statistically greater rate of success (complete/nearly complete resolution) at Week 24 in the propranolol 3 mg/kg/day for 6 month arm compared with the placebo arm (22.8% versus 3.6%, respectively, $p = 0.004$). However, while the success rates in the placebo group in the post hoc analysis and the primary analysis were identical (3.6%), the success rates in the propranolol 3 mg/kg/day for 6 month arm were markedly

discordant (22.8% versus 60.4%, respectively). The success rate in the propranolol 3 mg/kg/day for 6 month arm in the post hoc analysis of the investigator on-site assessment is consistent with the pre-specified secondary analysis of the investigator on-site assessment (22.8% and 26.7%, respectively). In both investigator-on-site assessments of the primary efficacy endpoint, the success rate in the propranolol 3 mg/kg/day for 6 month arm were markedly lower than that observed in the primary analysis, casting doubt on the reliability of centralised (photograph) assessment to accurately predict clinical outcomes.

3. In the pivotal study, there are data suggesting that propranolol 3 mg/kg/day for 6 months might improve the appearance of IH at Week 24 compared with placebo. However, the study was not designed to test the effect of propranolol on improvement, and all evidence suggesting that the proposed dose provides a treatment benefit relating to improvement at Week 24 is exploratory rather than definitive.
4. There are no pivotal data indicating that treatment benefits observed at Week 24 can be maintained following cessation of treatment. The available data suggesting that this might be the case are preliminary and considered to be exploratory.
5. In the pivotal study, the risks of treatment with propranolol 3 mg/kg/day for 6 months for the proposed indication were notably greater than placebo. Therefore, in order for the benefit-risk balance to be favourable it is considered that treatment with propranolol 3 mg/kg/day x 6 months for the proposed indication must demonstrate unequivocal efficacy compared with placebo. For the reasons discussed above, it is considered that propranolol 3 mg/kg/day for 6 months has failed to demonstrate unequivocal efficacy compared with placebo. Consequently, the benefit-risk balance for propranolol 3 mg/kg/day for 6 months for the treatment of the proposed indication is unfavourable.

In the event the application was approved, the evaluator's recommendation regarding the *Indications* section of the PI was as follows:

It is recommended that wording of the indication be amended to read *'Treatment of low-risk, proliferating infantile hemangioma requiring systemic therapy in infants aged from 30 to 150 days'*. The pivotal study included only patients with low-risk IH, and patients with life-threatening HIs, function threatening IHs and complicated ulcerated IHs were specifically excluded from the study. Furthermore, in the pivotal study, on-site investigator assessment showed that complications arising from IHs were infrequent suggesting that the IHs were low risk. Therefore, it is considered that IHs should be specified in the indication as low-risk. There are no pivotal efficacy data in the submission in infants with high-risk IHs. The age of patients to be treated should be stated in the indication in order to draw attention to the fact that the pivotal study included only patients in this age range, and that there are no pivotal data on patients outside this age range.

Details of additional revisions to the PI recommended by the clinical evaluator are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), Hemangiol EU-RMP version 1.0 dated 27 February 2013 (data lock point 12 October 2012), which was reviewed by the TGA's Post-Marketing Surveillance Branch (PMSB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

Table 6: Summary of Ongoing Safety Concerns

Ongoing Safety Concerns	
Important identified risks	Bradycardia Prolonged atrio-ventricular conduction or intensification of an AV block Hypotension Hypoglycemia and related seizure Bronchospasm and bronchial hyper-reactivity reactions
Important potential risks	Cerebrovascular complication in case of Posterior fossa brain anomalies, hemangiomas, arterial anomalies and cardiac defects and coarctation of the aorta (PHACE) syndrome with SNC [central nervous system in French] involvement Hyperkalaemia in case of large ulcerated IH Potential risk of administration error
Important missing information	Off-label use Long-term effects

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

Important potential interaction: concomitant use of corticosteroids

Evaluator comment: Notwithstanding the evaluation of the nonclinical and clinical aspects of the safety specifications, the sponsor's report is satisfactory.

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed to monitor all ongoing safety concerns. Additional activities are proposed as follows:

- Specific questionnaires for important identified risks of hypoglycaemia and related seizure, and for bronchospasm and bronchial hyper-reactivity reactions.
- Drug utilisation study for potential risk of administration error, and for missing information of off label use, and long-term effects.

In addition, the pharmacovigilance plan included details of 2 ongoing follow-up:

- Study V0400SB201 is a Phase II/III pivotal clinical trial which includes an 18-month efficacy and safety follow-up after the 24 week treatment period. Results from the follow-up are expected in 2014.
- Long-term follow-ups are conducted on patients in the CUP (France) and other patients being treated for at least three months. Growth and neurological development at 1 and 2 years after cessation of the treatment are measured and analysed in six monthly reports.

Risk minimisation activities

With regard to the need for risk minimisation activities, the sponsor concludes: 'All of the safety concerns identified in module SVIII 'Summary of the safety specification' are considered for risk minimisation activities. It is to be noted that among the routine risk minimisation measures, the mentions reported in the leaflet for patient's parents including the handling information has been written with particular detailed information in order to minimise or mitigate these risks.'

Evaluator comment: The sponsor's approach is acceptable.

Risk minimisation plan

The sponsor proposes routine risk minimisation measures to mitigate all the identified safety concerns.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the PMSB first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor acknowledges that any relevant safety issues will be addressed in the RMP.	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
The sponsor should inform the TGA if its application is rejected or deferred by overseas regulatory agencies.	The sponsor commits to inform the TGA if its application is rejected or deferred by overseas regulatory agencies. To date, no rejection or deferral has been received for this application.	The sponsor's response is satisfactory.
An Australian Specific Annex (ASA) should be provided in support of the EU-RMP.	An updated version of Australian-specific annex (ASA), including information as requested by the PMSB, will be provided as an annex of the EU-RMP.	The sponsor's response is satisfactory. The sponsor should submit the updated ASA to the PMSB for review.
The sponsor should clarify which safety issues are targeted by the two ongoing follow-up studies as part of the pharmacovigilance plan.	In annex 4 (Ongoing and completed clinical trial programme) of the RMP provided to the TGA, Study V0400 SB 2 01 and Study V0400 SB 3 01 were ongoing. *Study V0400 SB 2 01*: Long term effects of Hemangiol are considered as important missing information in the EU RMP. Long term safety data are expected from Week 96 follow up of study V0400 SB 2 01. Surveillance for 18 months at least, including mental status, mental development, pulse, BP, ECG, and two dimensional cardiac ultrasound, lung and liver development and maturation could permit to obtain data on long term effects. The follow-up phase of the Study V00400SB201 is now completed. The last patient had his visit of Week 96 on 05-Nov-2013. *Study V0400 SB 3 01*: The objective of clinical Trial V0400 SB 3 01 was to allow the use of propranolol with adequate conditions of administration and follow up in patients judged as requiring this systemic treatment after participation to a previous trial (V00400SB201 or V00400SB102). The safety profile (including long-term impact) and the effect on the resolution of target proliferating IH were documented. However only 11 patients have been included and limited data are expected from the long term follow up of this study.	The sponsor's response is satisfactory.
It is noted that the drug utilisation study is planned as a postmarketing study in the EU. The sponsor should provide an alternative plan in case its application for registration in the EU is rejected or deferred.	The drug utilisation study (DUS) is planned to be conducted in France, Germany, Canada and Australia. However, should Hemangiol application be rejected or deferred in the EU, DUS will be conducted in selected countries where a marketing authorisation has been granted (including Canada and Australia).	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	As requested by the TGA, the sponsor commits to provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	The sponsor's response is satisfactory.
In addition to interim and final reports, findings regarding safety specification and adverse events from the studies are expected to be reported in the Period Safety Update Reports (PSURs) and submitted to the TGA.	As requested by the TGA, the sponsor commits to report any findings regarding safety specification and adverse events from the studies in the PSURs/Periodic Benefit-Risk Evaluation Report PBRER) and to submit these reports to the TGA.	The sponsor's response is satisfactory.
It is noted that isoprenaline and aminophylline have been suggested for managing bronchospasm caused by Hemangiol overdose. It is recommended that the Delegate assesses the choice of drugs, especially considering the safety and the possible lack of experience among prescribers of using aminophylline in infants. It is also recommended to the Delegate that the name 'isoprenaline' should be used instead of 'isoproterenol' as the former is the generic name appearing on the ARTG.	The name isoprenaline will be used instead of isoproterenol in the Australian PI. As a matter of fact, the recommendations for the management of bronchospasm [are included] in the Prescriber's Information of Inderal in Australia Similarly to the Australian PI of Inderal, the use of aminophylline in bronchospasm is also recommended in the PI of Inderal in the US and Syprol in the UK, both authorised in pediatric use. Conclusion: The sponsor proposes to modify the recommendation of bronchospasm treatment in the [PI] section Overdosage[43].	The sponsor's response is satisfactory. The evaluator acknowledges the fact that use of isoprenaline and aminophylline for bronchospasm caused by propranolol in paediatric patients has been broadly recommended in the PI for propranolol products in Australia and overseas. However, using aminophylline in infants remains a cause of concern due to the safety and the possible lack of experience among prescribers. Therefore, the recommendation remains to the Delegate that the choice of drugs for treating bronchospasm caused by propranolol in infants should be assessed.

Outstanding issues in relation to the RMP

- The sponsor should submit the updated ASA to the PMSB for review.
- The use of aminophylline in infants remains a cause of concern due to the safety and the possible lack of experience among prescribers. Therefore, the recommendation remains to the Delegate that the choice of drugs for treating bronchospasm caused by propranolol in infants should be assessed.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

[43] Details of proposed text in product labelling are beyond the scope of the AusPAR.

Comments on the safety specification of the RMP

Clinical evaluation report

The Office of Medicines Authorisation (OMA) of the TGA has provided the following comments in the CER:

'Overall, the clinical aspects of the Safety Specification in the draft RMP (initial submission) were acceptable, but the information on monitoring following initiation of treatment and each dose increase should include assessment of HR and BP for at least 4 h following dosing.'

Evaluator comments: The evaluator supports the comments made by the clinical evaluator. It is recommended to the Delegate that instructions are added under 'Dosage and administration' section of the PI.

Nonclinical evaluation report

The Office of Scientific Evaluation (OSE) of the TGA has provided the following comments in the nonclinical evaluation report:

'Results and conclusions drawn from the nonclinical program detailed in the sponsor's draft RMP (Part II) are in general concordance with those of the nonclinical evaluator except for the following reversible findings in the juvenile rat study, which are considered clinically relevant:

- *Decreased blood platelet counts.*
- *Decreased urinary output.*
- *Increased plasma triglycerides level.'*

Evaluator comments: The evaluator supports the comments made by the nonclinical evaluator. These safety concerns appear to reflect some of the class effects of beta blockers. If future evidence indicates higher incidence of severe AEs associated with the use of the product than other beta blockers, further investigation would need to be conducted.

Recommendation

The following should be included as a condition of registration:

- Implement Hemangiol EU-RMP version 1.0 dated 27 February 2013 (data lock point 12 October 2012) with ASA and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Orphan designation

Propranolol hydrochloride, was designated an orphan drug for '*the treatment of proliferating infantile hemangiomas requiring systemic therapy*' on 3 October 2012.

Delegate comment: The calculation of prevalence for the Orphan Drug designation was based on the group of infants with high-risk lesions.

Outline of submission

The clinical dossier comprised:

- One Phase I comparative bioavailability/bioequivalence study in healthy adult males (Study 1012A)
- One Phase I dose finding study (Study 102); population PK analysis and initial tolerability study in infants
- One Phase II/III pivotal study of efficacy (Study 201). Safety data was provided from studies 102 and 201 as secondary endpoints.
- Safety summary from a CUP in France.
- The submission also included a large quantity of published literature, predominately observational and non-randomised studies. At the pre-submission planning phase, the sponsor did not request evaluation of a literature based submission and therefore this part was not evaluated by the clinical evaluator.

Delegate comment: The literature was selected by the sponsor and did not comply with the TGA requirements for a pre-approved search strategy.

Quality

The chemistry evaluator highlighted that the sponsor removed a weight restriction from the proposed PI for infants less than 2kg.

The lowest dose that can be drawn up using the sponsor-provided syringe is 0.3 mL, this equates to the initial dose for a 2.25 kg infant of 0.5 mg/kg twice daily. There is a risk of overdose if infants of < 2.3kg are dosed using this syringe due to measurement error.

Delegate comment: For the safe administration of Hemangiol using the sponsor-provided syringe, it should be restricted to infants of weight ≥ 2.5 kg.

The chemistry evaluator raised concern regarding the excipient propylene glycol in Hemangiol, which will be administered at a dose of 2.08 mg/kg/day. Propylene glycol is metabolised by alcohol dehydrogenase which is saturated at 20 mg/kg in human neonates. The recommended European Standard for propylene glycol exposure is 4.58 mg/kg/day in human neonates, therefore the dose administered from Hemangiol alone is considered safe. However, propylene glycol is contained in two other registered paediatric solutions. Concurrent administration of either of these two medicines may result in an unsafe propylene glycol exposure.

The sample child resistant cap, and bottle, supplied by the sponsor has not been satisfactorily demonstrated to be child resistant under conditions where the cap becomes coated with product. The sponsor was due to present a study of such conditions after the end of the evaluation phase of the submission but this was not submitted prior to this overview.

Delegate comment: Without the study of the child resistance of the container, the Delegate considers the standard of packaging to be not satisfactorily demonstrated.

The microbiology evaluator had no objections to the registration.

Nonclinical

There were no nonclinical objections to the registration of Hemangiol for the proposed indication.

Clinical

Pharmacology

Study 1021A demonstrated that the requirements for bioequivalence of the tablet and oral solution formulations were met, with dose normalised propranolol plasma concentration-time profiles being similar for two formulations; $AUC_{0-\infty}$ was higher for the solution.

Pharmacokinetics

Study V0400SB 102 (Study 102)

This was an open label, single arm PK study of 3 mg/kg/day Hemangiol for 3 months.

The primary objective was: 'To characterise the PK of Hemangiol at steady-state in patients during treatment for proliferating IH requiring systemic therapy'.

Secondary objectives were:

- To characterise the PK of a propranolol metabolite (4-OH-propranolol).
- To assess the efficacy of Hemangiol on the evolution of the target IH over 12 weeks.
- To document the safety profile of Hemangiol in the treatment of IH.

Study 102 evaluated the time of steady state PK after treatment initiation between two groups aged 35-90 days or 91-150 days. Treatment was up-titrated using 1 mg/kg/day for 7 days, then 2 mg/kg/day for 7 days and 3 mg/kg/day for 7 days.

In Study 102, the geometric mean Hemangiol steady-state Cmax levels and Tmax were similar in the two exposure age-groups. However, the mean $AUC_{0-9\ h}$ was higher in the younger age group. The population PK analysis supported dosing using mg/kg rather than age of the infant.

The infants enrolled into this study had high-risk lesions, that is, those that were function threatening, life threatening, or were severely ulcerated. Of the 23 infants enrolled, seven patients had 10 complications at baseline. These baseline complications were reported to have resolved by assessment after 28 days of treatment, except in one infant with grade 1 ulceration. The sponsor states that 'all patients were clear of complications by Visit 6 (Day 56) and remained clear at Visit 7 (Day 84)'. The details of the baseline complications of the seven patients were provided in the sponsors' response to the second round CER[44].

Delegate comment: The PK profile of Hemangiol was only evaluated in infants with high-risk lesion(s). There may be substantial differences in PK between infants with a solitary low-risk IH lesion and subjects with high-risk lesion(s), particularly in the liver, that have not been identified by this small study.

Efficacy

Pivotal Study V0400SB 201 (Study 101)

This was an adaptive, multicentre, randomised, double-blind placebo controlled Phase II/III clinical efficacy and safety study in infants aged 30 to 150 days.

[44] The sponsors' response to the second round CER contains the sponsor's identification of errors and omissions in the final CER. The document is not included in the AusPAR but comments in it are taken into account in the Delegate's overview.

The primary study objective (as per the SAP) was: 'To identify the appropriate dose and duration of Hemangiol treatment and demonstrate its superiority over placebo based on resolution of target IH at Week 24'. Treatment efficacy was assessed using the intention to treat (ITT) population.

This was re-worded in the sponsor's *Summary of clinical efficacy* as: 'The primary efficacy analysis compared the complete/nearly complete recovery rate issued from centralised assessment at Week 24 on the selected regimen of propranolol to placebo on the intent to treat (ITT) data set'.

Of note, cross-over from placebo to active treatment was permitted, and occurred, prior to the primary efficacy assessment point (Week 24 of treatment).

Secondary objectives were:

- To assess the safety profile of the 4 regimens of Hemangiol in treatment of IH in infants aged 1 to 5 months (35 to 150 days) at inclusion.
- To document the long-term follow-up of patients for 72 weeks after study treatment discontinuation (in terms of efficacy and safety).

Delegate comment: The long-term follow-up data is not reported in the dossier.

This study comprised two stages:

Stage 1 had five arms: Hemangiol 1 mg/kg/day for 3 or 6 months, 3 mg/kg/day for 3 or 6 months, and a placebo arm, randomised 2:2:2:1 respectively.

The interim analysis at the end of stage 1 was to determine the 'best' regimen of Hemangiol, when 35 randomised patients had completed their Week 24 follow-up visit. The 'best' regimen was defined as: 'the most efficacious out of all the regimens with a good safety profile' in the SAP.

Delegate comment: The 'most efficacious' regimen was determined using the treatment response criteria shown in Table 9 below, which is an amalgamation of several potential outcomes, with differing clinical significance. The same criteria were used to assess efficacy of stage 1 and stage 2. The Delegate cannot determine the sponsors' definition of a 'good safety profile' from the dossier.

Stage 2 had two arms: the 'best' Hemangiol regimen from stage 1 and a placebo arm; subjects were randomised 2:1 respectively in this stage. Patients recruited to the three stage 1 Hemangiol arms that were not determined to be the 'best' were not included in the final efficacy analysis but were included in the safety set.

Subjects were eligible if they were treatment naïve; had a proliferating hemangioma requiring systemic therapy anywhere on the body except the diaper (sic) area with largest diameter of at least 1.5 cm; the patient was aged 30 to 150 days old. Premature infants were only eligible when their corrected postnatal age was at least term + 5 weeks.

The following risk criteria (as described in the sponsor's response to the TGA request for information) were documented to further clarify the study entry criteria (Table 8).

Table 8: IH criteria for inclusion in pivotal study

Target IH - indications for inclusion in pivotal study	Risk stratification	Permitted inclusion in Study 201
Life- and function-threatening IH	High	NO

Target IH - indications for inclusion in pivotal study	Risk stratification	Permitted inclusion in Study 201
IH in certain anatomical locations that often leave permanent scars or deformity, especially the nose, lip, ear and glabellar area	Low	YES
Large facial IH, especially those with a prominent dermal component (more likely to leave permanent scarring)	Low	YES
Smaller hemangiomas in exposed areas, such as the faces and hands, may be considered for treatment with modalities unlikely to cause scarring or significant side effects	Low	YES
[non-severe] Ulceration	Low	YES
Severe ulcerated IH (whatever the localisation) with pain and/or lack of response to simple wound care measures	High	NO
Pedunculated hemangiomas (likely to leave significant fibrofatty tissue after involution)	Low	YES
IH with a potential risk of disfigurement	Low	YES

Additional exclusion criteria of note were: where the diagnosis was not clinically certain or Posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome (PHACES). The complete list of exclusion criteria provided in the dossier was noted.

Statistical plan

Stratified block randomisation was performed with two strata of: chronological age of the infant (dichotomised as 35-90 and 91 to 150 days) and IH site.

Delegate comment: The age of the lesion was recorded, but was not a randomisation factor, despite it being a significant confounder.

First stage: The SAP states 'Assuming that one regimen of Hemangiol is selected after the first 35 randomised patients completed their Week 24 follow-up visit or withdrawn from the study' and 'the 'best' regimen of propranolol (the most efficacious out of all the regimens with a good safety profile) is selected by the IDMC'.

Second stage: The SAP states that the objective of this stage is to demonstrate superiority of the selected regimen.

Sample size: the SAP states: an analysis of 85 evaluable patients per treatment arm over the two stages of the study (placebo and the selected regimen[s] of propranolol) would provide more than 90% power to test for superiority of propranolol over placebo with a 0.005 overall one-sided Type I error rate.

With regard to missing data, the SAP states: 'Where data are missing, we will report the number of observations when missingness (sic) is important; we will not impute missing values unless specified otherwise'.

Delegate comment: As described below, there are a number of subjects in the pivotal study with missing efficacy evaluations, the sponsor has chosen to define the outcome of all missing subjects in the placebo arm as 'treatment failures', but has not applied the same definition to the Hemangiol-assigned group.

Assessment of treatment effect

The primary efficacy assessment was performed by two blinded central observers who had been given 'special training' to evaluate photographs of the lesions taken at baseline and subsequent evaluation points. The response criteria for the blinded and on-site assessors are shown in Table 9.

Secondary assessment was reported by both the on-site clinicians and parents/guardians. The on-site observers used a very similar assessment method to the blinded assessors (see Table 9).

Delegate comment: The 'special training' given to the blinded observers is not described by the sponsor.

The Week 24 assessment was transformed into a binary outcome of 'success' or 'failure' by the sponsor, with 'success' being a composite of all the subjects that fulfilled any of the criteria in table 2 below for the purposes of the statistical analysis.

Table 9: Categorisation of treatment response

Binary outcome at Week 24 assessment	Central observer (photographic assessment)	On-site observer (clinical assessment)
Treatment 'success'	Complete resolution without sequelae	Complete resolution without sequelae
	Complete resolution with minimal sequelae	Complete resolution with minimal sequelae
	Complete resolution with marked sequelae	Complete resolution with marked sequelae
	Nearly complete resolution, with a minimal degree of the components: Telangiectasis Erythema Skin thickening Soft tissue swelling Distortion of anatomical landmarks	Nearly complete resolution, with a minimal degree of the components: Telangiectasis Erythema Skin thickening Soft tissue swelling Distortion of anatomical landmarks Palpable component
Treatment 'Failure'	Any other outcome	Any other outcome

Delegate comment: The potential outcomes that may determine treatment 'success' are very broad and not of equal clinical significance. The Delegate cannot determine what is meant by 'minimal degree' of each of the items under 'nearly complete resolution'. These criteria and the assessment methods are explored extensively in the discussion.

In total, 460 subjects were randomised to one of the five treatment arms.

At the end of stage 1, after 25 placebo-assigned and 35 Hemangiol-assigned subjects had been treated, the sponsor evaluated the Hemangiol regimen of 3 mg/kg/day for 6 months as the 'best', which formed the comparator with the placebo group.

Of note:

- The proportion of the placebo group patients in stage 1 completing their assigned treatment to Week 24 assessment was 6/25 (24%).
- 19/55 (35%) of the placebo group and 88/102 (88%) in the Hemangiol group completed their assigned treatment up to the primary efficacy assessment point of Week 24 of treatment.

Delegate comment: The SAP required 35 patients to have completed their Week 24 follow-up assessment. The denominator of placebo-assigned patients, and the proportion of patients assigned to placebo continuing to Week 24 was therefore inadequate to determine the 'most efficacious' regimen. The proportion of patients in the placebo arm that continued placebo until the primary efficacy assessment was 24%, this is also considered inadequate.

Despite the proportion of subjects not completing their assigned treatment regimen, the sponsor has reported the primary and secondary outcomes according to the ITT population, which was the pre-specified population for efficacy assessment.

Table 10: Week 24 primary efficacy assessment results

Week 24 assessment, ITT population				
		'Success'	'Failure'	P-value
Central observer	Placebo, n=55	2 (3.6%)	53 (96.4%)	P < 0.0001
	Hemangiol, n=101	61 (60.4%)	40 (39.6%)	
On-site observer	Placebo, n=55	2 (10.5%)	17 (89.5%)	P = 0.4419
	Hemangiol, n=101	24 (26.7%)	66 (73.3%)	

Delegate comment: In total 36/55 (65%) of all subjects in the placebo arm discontinued their treatment prior to the primary efficacy assessment at 24 weeks. Cross-over of placebo patients to active treatment occurred.

Furthermore, the Delegate identified that 26 subjects (47%) in the placebo arm and 11 subjects (11%) in the Hemangiol arm did not have efficacy assessments at Week 24. All of the 26 placebo subjects were considered to be 'treatment failures' despite not having evaluable assessment data. See Table 12 below.

There is a substantially different assessment of Hemangiol efficacy reported by the blinded and on-site observers. The on-site observers reported no difference in outcome between the Hemangiol 3 mg/kg/day arm and placebo arm.

With regard to the discrepancy of the efficacy outcome assessment between the central and on-site observers, the sponsor stated in the response to the TGA request for information that it 'cannot be explained by a lack of validity of the primary endpoint'. The clinical evaluator was of the opinion that the difference in observed outcomes is relevant, and can be explained

by the lack of validity of the primary end-point assessment method. The only difference in the efficacy assessment was that the on-site assessors could also evaluate the lesion deep component (by palpation).

Delegate comment: The Delegate concurs with the clinical evaluator's opinion that the difference in reported outcomes is extremely relevant. The minor difference in assessment method used by the different observers is not sufficient to explain such discrepant outcomes. The Delegate has to take the conservative outcome, that of the on-site assessors, as being the demonstrated treatment effect. See *Discussion* below.

The sponsor presented the following table of outcomes in the response to the TGA request for information:

Table 11: Week 24 assessment results

Primary endpoint: Complete or nearly complete resolution of target IH at week 24				
		Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	P value
ITT set	**Overall/combined**			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	2 (3.6%)	61 (60.4%)	
	No	53 (96.4%)	40 (39.6%)	
PP set	**Overall/combined**			
	n/missing	53 / 0	93 / 0	<.0001
	Yes	1 (1.9%)	56 (60.2%)	
	No	52 (98.1%)	37 (39.8%)	
Planned sensitivity analysis of ITT set*	**Overall/combined**			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	15 (27.3%)	62 (61.4%)	
	No	40 (72.7%)	39 (38.6%)	
Unplanned post-hoc sensitivity analysis of ITT set	n/missing	55 / 0	101 / 0	<.001
	Yes	17 (30.9%)	62 (61.4%)	
	No	38 (69.1%)	39 (38.6%)	

CSR Tables 18, Table 19 and Table 105, and UNPL_central_Response_ANA_sens2
* For patients who prematurely discontinued the study drug:
- If the patient was withdrawn from study therapy for treatment intolerance, the primary endpoint remained a failure.
- If the patient was not withdrawn from study therapy for treatment intolerance:
- If the closest centralized assessment (Type 2) from the end of treatment confirmed stabilization or worsening, the primary endpoint remained a failure.
- If the closest centralized assessment (Type 2) from the end of treatment did not confirm stabilization or worsening, 50% of the patients concerned in each treatment group were selected at random and their primary endpoint was redefined as a success.

Using data supplied in the sponsor's response to TGA request for information, the Delegate has populated the following table:

Table 12: Data populated from the CSR and sponsor's response

	Placebo	Hemangiol 3 mg/kg/day
Number initially randomised, n	55	102
Number that received randomised treatment	55	101
Number of patients that continued their assigned treatment to primary evaluation time point. n (% of those that received randomised treatment)	19/ 55 (35%)	88/101 (87%)
Number of patients that discontinued assigned treatment	36 (65%)	13 (13%)

	Placebo	Hemangiol 3 mg/kg/day
prior to primary efficacy evaluation. n (% of those that received randomised treatment)		
Cross-over to other treatment arm. n (% of those that received randomised treatment)	36/55 (65%)	Not reported
Patients with evaluable data at primary efficacy assessment point - week 24 of treatment. N (% of those that received the randomised treatment)	29/55 (53%) (19/19 patients that continued assigned placebo treatment and 10/36 patients that had discontinued placebo treatment and crossed over to active treatment)	88 (88%)

Delegate comment: Given the data presented in Table 12, there is conflicting evidence between the CSR and the sponsor's response to the TGA request for information. In Table 11 above, there are no 'missing' subjects in either the ITT population, per-protocol population or for the population used the sensitivity analysis of the primary efficacy endpoint assessment. The data from the sponsor's response to the TGA request for information shows that 22 (40%) patients in the placebo group and 13 (12%) patients in the Hemangiol group did not have evaluable data at the primary efficacy assessment point.

The criteria for exclusion from the per-protocol set included: administration of beta-blockers, or other treatments, and a lack of assessment at Week 24. Of the 36 subjects that did not complete 24 weeks in the placebo arm, the sponsor states that 'All of them have been treated with oral off-label propranolol or other beta-blocker' (sponsor's response to the TGA request for information). Hence, the cross-over subjects received prohibited treatments and were ineligible to remain in the per-protocol population. It is uncertain whether cross-over occurred prior to the primary efficacy evaluation, but to be conservative, the Delegate has assumed that this was the case. The issue of cross-over is dealt with in the *Discussion*, below.

Furthermore, it clearly states that of the 36 patients who prematurely left the placebo arm of the study only 10 had a Week 24 evaluation; the rest must therefore be considered missing and not evaluable.

(Supportive) Study 102

Efficacy data (observational) was available for 22 of the 23 infants treated with the proposed dose of Hemangiol of 3 mg/kg/day. An improvement in the appearance of the target lesion (complete or nearly complete resolution) was reported by the sponsor in 16/22 (72.7%) infants at Day 84 of treatment. No patients were reported as having a worsening of their lesion appearance.

(Supportive) Compassionate Use Program

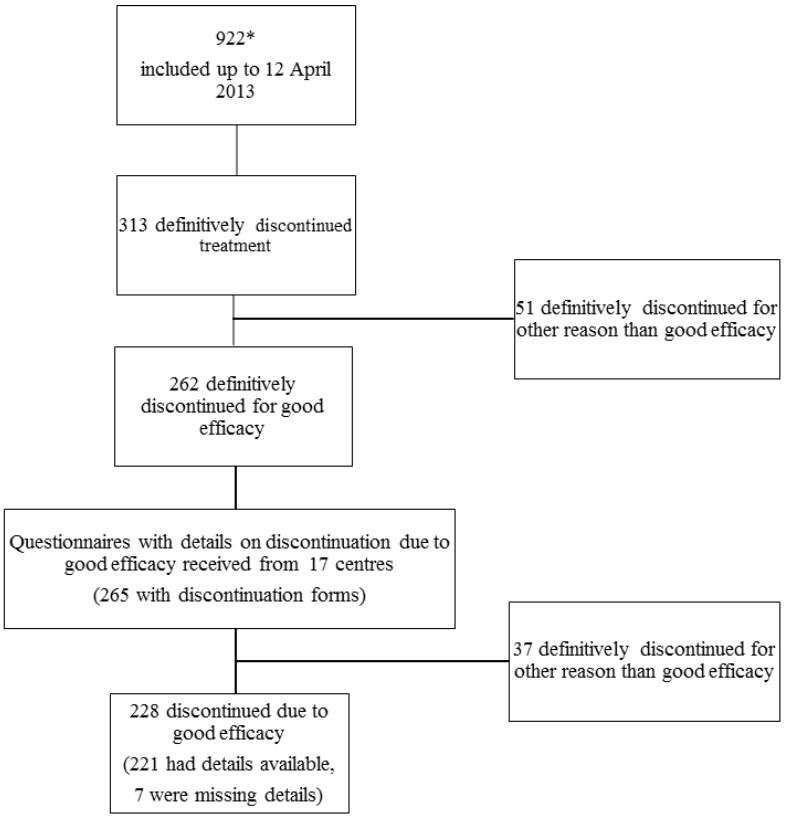
The use of Hemangiol in the CUP allowed infants with more severe grades of IH to be treated, including those with life threatening or function threatening lesions. The dose of Hemangiol used in the CUP was 2 mg/kg/day, but could be increased to 3 mg/kg/day 'if required'. Reasons for increasing the Hemangiol dose are not documented.

In the sponsors' response to the second round CER, it states 'The CUP did not feature any prospective assessment of efficacy; therefore, efficacy could be indirectly estimated through the documentation of reasons for treatment interruption, systematically requested for all patients'. Only surrogate efficacy outcomes are presented, below, from the treatment discontinuation information.

Delegate comment: That efficacy was not prospectively assessed in the CUP precludes a meaningful assessment of efficacy in this population with high-risk lesions. Surrogate efficacy data, pertaining to reason for discontinuation of Hemangiol, is presented below. Additionally, there is substantial missing data from the CUP. Together, this does not represent a sufficiently rigorous pharmacovigilance registry of evidence for regulatory purposes to support Marketing Authorisation of Hemangiol.

In total, 922 infants have been treated under the CUP. The disposition of the subjects is shown in Figure 3.

Figure 3: Outcomes from the Compassionate Use Program



The sponsor does not report any outcomes of the 609 subjects that did not 'definitely discontinue treatment'.

Delegate comment: Some 609/922 (66%) subjects do not have data evaluable for safety or surrogate efficacy.

The data presented for the 313 subjects documented to have 'definitely discontinued treatment' revealed:

- 262/313 (84%) had the duration of treatment documented.
- 202/922 (21.9%) received at least one dose of Hemangiol at 3 mg/kg/day.
- Of 71/922 (7.7%) received Hemangiol at 3 mg/kg/day (the proposed dosage) and had documentation on efficacy, 49/71 subjects had a complete/nearly complete response.

The maximum subject age was 1913 days (5.2 years)

Delegate comment: The reason for including a child of this age into the CUP is not presented.

In regard to the CUP patients, the sponsor states: 'In line with the general population, (77.0%) patients were female'.

Delegate comment: The meaning of this statement is uncertain, given 50% of the general population are female.

The reasons for discontinuation are only reported for the 313 patients that 'definitely discontinued treatment':

- 262/313 (83.7%) discontinued due to good efficacy;
- 18 patients (5.8%) discontinued due to an AE;
- 11 patients (3.5%) discontinued due to contraindication;
- 11 patients (3.5%) discontinued due to inefficacy;
- 18 patients (5.8%) discontinued due to other reasons

  (Multiple reasons for discontinuation were included).

Delegate comment: It is of concern that 11 patients definitively discontinued Hemangiol due to a contraindication. It is not clear whether these contraindications were present at the time of treatment initiation or whether they evolved on-treatment.

Of the 313 patients described, only 265 (85%) had 'documented data on discontinuation in the centres with complete detailed information on discontinuation for good efficacy'. IH was reported as 'completely recovered' or 'almost completely recovered' in 154/313 (49.2%) subjects and 50.8% had either not recovered or had missing data.

Delegate comment: The response to treatment was not prospectively assessed. The 'efficacy' response was determined from (incomplete) documentation on reasons for discontinuation. The vast majority of subjects 851/922 (92%) did not receive Hemangiol according to the proposed regimen of 3 mg/kg/day.

Safety

In total, 1084 subjects were included in the analysis of safety (424 pooled from studies 102 and 201, plus 660 from the French CUP).

There were no deaths reported in the pooled safety population.

The sponsor provided an unsolicited update of 'efficacy' from the CUP in the response to second round TGA evaluations, but this did not include any new safety data.

Delegate comment: The sponsor has presented the safety data from the pivotal study of efficacy according to the initial treatment assignation. As discussed above, there is a substantial proportion of the placebo-assigned arm that crossed over to active treatments. It is therefore uncertain what the true denominator of patients in each arm is, given that these other treatments have not been reported.

Only patients that did not end treatment prematurely had follow-up assessments. As discussed above, only 33/55 (60%) patients in the placebo arm continued treatment until the Week 24 assessment point. From the data presented, it is not certain what the safety profile was of the patients that crossed over from placebo to active treatment in Study 201.

Table 13: Summary of TEAEs

	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)
Patients with at least one AE	41 (74.5%)	90 (91.8%)	90 (88.2%)	91 (91.0%)	96 (95.0%)
Patients with at least one TEAE	40 (72.7%)	89 (90.8%)	90 (88.2%)	91 (91.0%)	96 (95.0%)
Patients with one TEAE	13 (23.6%)	18 (18.4%)	16 (15.7%)	12 (12.0%)	16 (15.8%)
Patients with two TEAEs	7 (12.7%)	10 (10.2%)	6 (5.9%)	9 (9.0%)	13 (12.9%)
Patients with more than two TEAEs	20 (36.4%)	61 (62.2%)	68 (66.7%)	70 (70.0%)	67 (66.3%)
Patients with at least one AE leading to definitive study drug discontinuation	6 (10.9%)	4 (4.1%)	2 (2.0%)	7 (7.0%)	3 (3.0%)
Patients with at least one related TEAE	16 (29.1%)	44 (44.9%)	33 (32.4%)	35 (35.0%)	35 (34.7%)
Patients with at least one Serious AE	3 (5.5%)	5 (5.1%)	3 (2.9%)	9 (9.0%)	6 (5.9%)
Occurrence of TEAEs	143	516	478	468	520
Occurrence of AEs leading to definitive study drug discontinuation	7	4	2	10	3
Occurrence of related TEAEs	31	147	81	71	75
Occurrence of serious AEs	3	5	5	13	7

Overall, the proportion of subjects with at least one TEAE leading to temporary discontinuation was higher, and dose dependent, in the Hemangiol groups than placebo: 4.2% placebo, 9.5% Hemangiol 1 mg/kg/day, and 15.2% Hemangiol 3 mg/kg/day.

The majority of patients in the Hemangiol groups experienced at least 3 TEAEs.

Hypoglycaemia

The sponsor states in the pivotal study CSR that two subjects experienced hypoglycaemia, whereas three have been identified by the Delegate.

Hypoglycaemia was defined by the sponsor to be 2.2 mmol/L (40 mg/dL) for the purposes of determining if intervention was required, that is, temporary or permanent discontinuation of study drug (sponsor's response to the TGA request for information).

The two sponsor-identified subjects had both been treated with Hemangiol (two each received 1 mg/kg/day and one received 3 mg/kg/day).

One patient in the 1 mg/kg/day arm had a blood sugar level of 1.9 mmol/L measured at the Week 24 assessment point.

A total of five subjects in the safety population were reported as having had seizures attributed to hypoglycaemia secondary to Hemangiol use.

Delegate comment: The definition of hypoglycaemia in current use is 2.6 mmol/L. The sponsor was specifically asked in the *Clinical Questions* to respond to the question of the definition of hypoglycaemia. The sponsor stated that a glucose level of 2.2 mmol/L was 'lower that one of the accepted normal range value for blood glucose' and re-iterated that it 'was defined as the point for intervention'. By choosing a lower limit to treat hypoglycaemia than is currently recommended, subjects recruited into the study have been exposed to an unacceptable increase in risk of hypoglycaemia, seizure and adverse neurodevelopmental outcome. (See also below for further discussion).

Overdose

Two patients in the pooled safety population were reported to have been exposed to an overdose of study medication, one in each of the placebo and 1 mg/kg/day arms. No AEs were reported in association with either.

Seizure was reported in association with overdose in the whole safety population.

Bradycardia

The threshold definition for responding to bradycardia changed over the course of the study. The Day 0 definition was < 80 beats per minute (bpm), whereas the definition was < 60 bpm for the Day 7 and Day 14 assessment prior to up-titration:

Table 14: Heart-rate criteria for dose delay or discontinuation

Action to be taken	D0 – pre-dose	D7 and D14 – pre-titration	D0, D7 and D14 – 4 h safety assessment
Do not give study therapy (pre-dose/pre-titration) and continue to monitor the patient on site	HR < 80 bpm or	HR < 60 bpm or	
Permanently discontinue study treatment and continue to monitor the Patient on site	1) After further monitoring (before dosing): HR remains < 80 bpm	1) After further monitoring (before dosing): HR remains < 60 bpm	1) After further monitoring (beyond the scheduled 4 h): HR remains < 60 bpm
		2): At any time before dosing: HR < 50 bpm for > 1 min	2): At any time after dosing (beyond the scheduled 4 h): HR < 50 bpm for > 1 min

The proportion of patients in each randomisation arm experiencing bradycardia < 80bpm, by treatment arm is reported as:

Table 15: Episodes of bradycardia by treatment arm

	Placebo 6mths n=55	V0400SB 1mg/kg/day 3mths n=98	V0400SB 1mg/kg/day 6mths n=102	V0400SB 3mg/kg/day 3mths n=123	V0400SB 3mg/kg/day 6mths n=101
1: At least one HR <80 bpm during treatment period	3 (5.5 %)	7 (7.1 %)	6 (5.9 %)	18 (14.6 %)	15 (14.9 %)
2: At least one HR <80 bpm during up-titration period	3 (5.5 %)	4 (4.1 %)	2 (2.0 %)	11 (8.9 %)	9 (8.9 %)
3: At least one HR <80 bpm after up-titration period	-	5 (5.1 %)	5 (4.9 %)	7 (5.7 %)	12 (11.9 %)

The is an apparent dose-response effect on bradycardia incidence, however the denominator of both treatment arms is uncertain due to cross-over and loss to follow-up.

ECG abnormalities

First-degree heart block (PR interval >160 ms) was more common in the Hemangiol arm of Study 201 and the pooled safety population:

Table 16: PR interval > 160 ms in Study 201 safety population by treatment regimen

	Placebo 6mths n=55	V0400SB 1mg/kg/day 3mths n=98	V0400SB 1mg/kg/day 6mths n=102	V0400SB 3mg/kg/day 3mths n=123	V0400SB 3mg/kg/day 6mths n=101
1: At least one PR >160 msec during treatment period	1 (1.8 %)	-	-	5 (4.1 %)	3 (3.0 %)
2: At least one PR >160 msec during up-titration period	1 (1.8 %)	-	-	5 (4.1 %)	2 (2.0 %)
3: At least one PR >160 msec after up-titration period	-	-	-	1 (0.8 %)	1 (1.0 %)

Table 17: PR interval > 160 ms in the pooled safety population

	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
1: At least one PR >160 msec during treatment period	2 (0.8 %)	-	8 (3.6 %)	8 (1.9 %)
2: At least one PR >160 msec during up-titration period	1 (0.4 %)	-	7 (3.1 %)	7 (1.7 %)
3: At least one PR >160 msec after up-titration period	1 (0.4 %)	-	1 (0.4 %)	1 (0.2 %)

Three patients permanently discontinued treatment due to abnormalities detected on routine ECG monitoring (QT prolongation, second degree AV block and bradycardia respectively).

Echocardiography

Routine echocardiography pre-treatment was performed on 517 patients and 17 patients did not have it performed. One patient was excluded from treatment on the basis of the results, a finding of an intra-cardiac mass.

Hypotension

In the sponsors' response to the second round CER, it is stated that: 'The [sponsor] does not consider that BP is an adequate tool for monitoring infantile patients after dosing with propranolol'.

In the pivotal study, hypotension was documented in six patients, five of whom were treated with Hemangiol and one in the placebo arm. The incidence of hypotension was equally split between the titration phase (first 3 weeks), in 3 patients including the subject in the placebo arm, and in 3 patients occurring between Day 21 and Week 12 of therapy.

No episodes were considered serious and none resulted in premature discontinuation.

Bronchospasm

The incidence of the TEAEs of bronchospasm and bronchiolitis were greater in the Hemangiol arm as compared placebo. Given that bronchiolitis has a virally mediated aetiology, the effect of Hemangiol in this disease is a not causative agent but worsens the response of the infant. Bronchiolitis occurs in a seasonal manner in Australia, with cases occurring more frequently in winter. A 6 month treatment period of Hemangiol will likely be associated with bronchiolitis exacerbations, and potentially hospitalisation, during this time.

Neurology

Two patients were reported as having an abnormal neurological examination in the pivotal study, both in the Hemangiol 1 mg/kg/day 3 month arm.

In the sponsor's SCS, it states: 'Neurodevelopment disorder: 1 patient in the 1 mg/kg/day 6 months regimen, after Week 12. The patient had an outcome of not recovered, recovering or missing.' The reported outcome for this subject is unsatisfactory.

One subject was reported as having a treatment-emergent SAE of epilepsy which led to study discontinuation. The reported outcome for this subject is not satisfactory: the description is of an 'anterior severe neurological disorder and epilepsy was not suspected to be related to

the study drug'. The sponsors' description of an 'anterior severe neurological disorder' does not represent an actual medical diagnosis and is therefore cannot be satisfactorily assessed for causality.

As regards neurological follow-up, the sponsor states that of 129 patients treated for at least 3 months and followed-up for one year, only 48 (37%) patients were reported to be assessable. Four of these were actually lost to follow-up and therefore not assessable, one patient had 'finally not received the treatment' and 43 'have not experienced any neurodevelopment disorder of growth delay'. The outcomes for the remaining 81 (63%) patients are therefore uncertain and cannot be assumed to have event-free survival.

A total of five subjects in the safety population were reported as having had seizures attributed to hypoglycaemia secondary to propranolol use, including as a result of inadvertent overdose of Hemangiol.

Clinical evaluator's recommendation

The clinical evaluator did not recommend registration of Hemangiol for the sponsor's proposed indication after either of the two rounds of evaluation (see *Clinical Findings*, *First Round Recommendation for Authorisation* and *Second Round Recommendation for Authorisation*, above).

Risk management plan

The RMP evaluation was incomplete at the time of writing the Overview, since the sponsor did not provide the EU-RMP for evaluation in time to be evaluated.

The RMP evaluator considered the RMP as satisfactory, with the identified and potential risks and important missing information as shown in Table 6 above.

In the RMP evaluation, there is a description of the long-term growth and neurological follow-up of infants treated for at least 3 months. As seen in the safety discussion above, the neurological follow-up is deficient as there is a large proportion of treated infants that have not been evaluated at the 1 year follow-up point.

The Delegate considers the 'important missing information – long-term effects' to be crucial to the decision to approve or reject the sponsors proposed indication.

The Delegate also considers that the important identified risk of 'seizure' should be added to the RMP.

The Delegate considers that the important potential risk of 'adverse neurodevelopmental outcome' should be added to the RMP.

Risk-benefit analysis

Delegate's considerations

The discussion will use as a reference the following documents:

- The sponsor's dossier
- The round 1 and round 2 CERs
- The sponsors' response to the TGA request for information and response to the second round evaluations
- The round 1 and 2 RMP evaluation
- The sponsors' response to the RMP evaluations

- TGA adopted EMA guidelines on:
  - Points to consider on application with 1. Meta-analyses; 2. One pivotal study' (CPMP/EWP/2330/99).
  - Points to consider on missing data (CPMP/EWP/1776/99)
  - Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)

Reasons for not recommending approval of Hemangiol for Marketing Authorisation:

Safety: Pivotal study

1. The clinical evaluator correctly states: 'the safety analysis of the pivotal study was undertaken on the safety data set which included 401 patients treated with propranolol and 55 patients treated with placebo'. Adverse events have only been reported according to the arm that the infant was originally randomised into, not whether they received the study drug, or other treatments. This analysis fails to take into account the fact that 36/55 patients in the placebo arm left the study early and received active treatments including beta-blockers (see efficacy discussion below). The effect of this method of reporting necessarily changes the true denominator of patients exposed, in both the placebo and treatment arms. The true incidence of AEs in the placebo arm is therefore uncertain as the reporting method may have minimised the differences in incidence of adverse outcomes as compared to the Hemangiol treatment arm(s). Furthermore, only 33/55 (60%) of patients in the placebo arm continued the assigned treatment to the follow-up period. This very large proportion of patients lost to follow-up, of an initially small group of patients, is unsatisfactory from a regulatory point of view and precludes a meaningful assessment of safety from the pivotal study.
2. Despite the long-standing use of propranolol in infants, there is no published literature confirming that there is no adverse long term effect of the medication on neurocognitive development in this age group. In particular, safety has not been satisfactorily established for the group of infants with low-risk cutaneous IH where there is no additional risk for abnormal neurocognitive development other than the Hemangiol treatment itself. The safety of propranolol use in other indications, such as infants with congenital heart disease, is not directly comparable with those with low-risk IH as there are confounding effects of the disease of indication and surgery in these other indications[45].

   It is anticipated that given the exposure to Hemangiol in otherwise healthy infant subjects with low-risk lesions, long term formal neurodevelopmental follow-up would be performed in the pivotal trial, as per the *Guideline on Clinical Investigation of medicinal products in the paediatric population*. Only 43 out of 129 evaluable subjects treated with Hemangiol for at least 3 months have had neurological follow-up one year after treatment initiation. The pivotal study cannot therefore satisfactorily demonstrate a lack of adverse effect on neurodevelopmental outcomes from Hemangiol exposure. Furthermore, formal neurodevelopmental assessment of the infant subjects was not included as part of the pivotal study protocol, for example, by the Bailey Scale of Infant Development or Prechtel's assessment of general movements.
3. The definitions and management of hypoglycaemia employed in the pivotal study are not consistent with current clinical practice and yield uncertainty as to the true incidence of the condition and outcomes for those demonstrated to have had hypoglycaemia:
   i. Diagnosis of hypoglycaemia

[45] Gunn, J. et al. Perioperative amplitude-integrated EEG and neurodevelopment in infants with congenital heart disease. Intensive Care Medicine 2012:38(9);1539-1547

Patients only had their blood glucose measured during the up-titration phase on one occasion prior to the next incremental rise. This potentially exposed patients to one week of un-recognised asymptomatic hypoglycaemia. The effect of this method is that the true incidence of hypoglycaemia has potentially been under reported and is therefore not satisfactorily established.

ii. Incidence of hypoglycaemia

There is a discrepancy between the numbers of subjects identified by the sponsor and Delegate as having had hypoglycaemia, resulting in uncertainty of the true incidence of the AE.

iii. Outcomes of hypoglycaemic infants

The outcomes for the infants with low-risk IH that experienced hypoglycaemia have not been established to satisfactorily assess the risk. A specific pattern of occipital injury, and potential vision loss, as a result of hypoglycaemia is well recognised following hypoglycaemia in the neonatal period[46, 47]. It is not clearly described when this risk reduces in the post-neonatal period of the first year of life, this notwithstanding, there is a risk to any part of the developing brain from hypoglycaemia. In infants with low-risk IH treated with Hemangiol, occult hypoglycaemia may have occurred but not been identified, due to lack of neurodevelopmental follow-up, and therefore exposed these subjects to an unknown and unacceptable risk of cerebral injury and/or vision loss. Furthermore, in the pivotal study and according to the sponsor's response to the TGA request for information, it was mandated that treatment of hypoglycaemia be initiated following a serum glucose measurement of 2.2 mmol/L, which is below the standard accepted definition of hypoglycaemia of 2.6 mmol/L[48, 49]. For subjects with a serum glucose level between 2.2 and 2.6 mmol/L no treatment was mandated, thus exposing these subjects to an unacceptable risk of short and long term hypoglycaemic sequelae. The risk of hypoglycaemia was seen to extend to the Week 24 assessment point as reported in one patient, not just during the 3 week up-titration phase. Given that the effects of hypoglycaemia have neither been studied nor reported in the small population of infants treated with the proposed Hemangiol dose in the pivotal study, safety of Hemangiol has not been satisfactorily established.

4. The comparative safety profile of Hemangiol, as compared to other available treatments (such as timolol, corticosteroids, and vincristine) has neither been explored nor demonstrated by the pivotal study. This lack of evidence is particularly crucial in the setting of infants with low-risk cutaneous IH, and without cerebral lesions, where the natural history is for lesions to regress spontaneously during a concomitant phase of rapid, and potentially susceptible, cerebral development.

5. The reported number of subjects developing new lesion ulceration during the course of the pivotal study was greater in the Hemangiol arm 4/102 (3.9%) versus 2/55 (3.6%) with placebo. Given the possibility for patients to cross-over, it is uncertain if the placebo-assigned patients were actually receiving placebo at the time ulceration occurred. Therefore, it has not been satisfactorily demonstrated that Hemangiol reduced the risk of ulceration in previously non-ulcerated lesions in this study population. The sponsor has stated that 'scarring is inevitable if ulceration has occurred' (sponsor's Clinical overview). Given that ulceration was more commonly reported in the Hemangiol

[46] Filan et al. Neonatal hypoglycaemia and occipital cerebral injury. *J Pediatrics* 2006:148;552-555.
[47] Tam, E. et al. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycaemia. *Pediatrics* 2008:122; 507-512.
[48] Australian Resuscitation Council Guideline 12.4 Medications and fluids in paediatric advanced life support. 2010.
[49] Lucas A, Morley R. Cole T. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988:297;1304-1308.

arm, by the sponsors' own assertion, the incidence of scarring is necessarily increased as a result of Hemangiol exposure in this low-risk population. The degree of scarring has not been reported for any of these lesions, nor has the requirement for intervention to treat scarring.

6. The sponsor is of the opinion that BP measurement in infants is 'difficult to interpret', 'obtaining BP measurements in infants may be challenging' and 'the [sponsor] does not consider that BP is an adequate tool for monitoring infantile patients after dosing with propranolol' (sponsor's response to the CER). The Delegate considers these statements to be wholly unsatisfactory, given the routine use of BP monitoring in numerous paediatric settings by experienced clinical staff caring for infant patients. Hypotension was demonstrated to have occurred following Hemangiol use. The normal range for BP in infants is well established and is therefore not 'difficult to interpret'. The sponsor has removed the recommendation from the PI for the BP of treated infants to be assessed, despite it being stated that 'isolated cases of symptomatic bradycardia and hypotension have been reported in the literature'. There exists, therefore, a risk of hypotension following Hemangiol exposure which can only be, and should be, assessed by BP measurement.

Efficacy: Pivotal study

The guideline for a single pivotal study of efficacy documents that: the confirmatory evidence should demonstrate 'exceptionally compelling' confirmatory evidence, with prerequisites of:

i. with regards to internal validity 'there should be no indications of bias'

ii. with regard to external validity 'the study population should be suitable for extrapolation to the population to be treated'

iii. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect

1. Lack of adequate control arm

The pivotal trial allowed cross-over from placebo to active treatment prior to the primary efficacy Week 24 assessment point, invalidating the intention to treat principle. In total 36/55 (65%) subjects prematurely ceased the placebo and all subsequently received active treatment, including beta blocker (sponsor's response to the TGA request for information). Once patients have crossed over randomisation is broken, the subjects are no longer considered exchangeable, and the ITT population can no longer be used for comparisons. Given that cross-over has occurred prior to the primary efficacy evaluation point, the pivotal study can only be evaluated as a cohort study and the effect of active treatment cannot be satisfactorily compared with the spontaneous resolution rate in the placebo arm. Indeed the sponsor states, in regard to cross-over 'It is impossible to predict exactly what the outcomes at Week 24 would have been had these patients continued to receive the assigned study treatment' (Statistical methods and sponsor's response to the TGA request for information).

This situation is unsatisfactory for regulatory purposes and necessarily negates the sponsors' conclusions pertaining to demonstration of efficacy of Hemangiol since the ITT population was pre-specified to demonstrate the primary efficacy outcome. Furthermore, after excluding the cross-over subjects, there is differential loss to follow-up between the treatment arms: only 19/55 (34%) subjects in the placebo arm and 86% subjects in the Hemangiol arm completed treatment until the Week 24 assessment point, which greatly exceeds the pre-specified level of 5% in the SAP. This differential loss to follow-up also precludes the use of an ITT analysis, as it biases the outcome in favour of active treatment and thus fails to adhere to the Guideline for a single pivotal study[50]. The overall denominator of 19 patients in the

[50] Hernan, M. Hernandez-Diaz, S. Beyond the intention-to-treat in comparative effectiveness research. *Clinical Trials* 2012:9;48-55

placebo arm with efficacy assessments is substantially lower than that required in the SAP and therefore insufficient for the demonstration of efficacy.

These features of the single pivotal study demonstrate a lack of internal validity which consequently affects external validity and generalisability, contrary to the requirements in the Guideline on a single pivotal study. The overall effect of these deficiencies is to preclude the demonstration of 'exceptionally compelling' evidence.

2. Missing data

There are significant discrepancies in the data presented with regard to missing subjects. The information contained in the sponsor's response to the TGA request for information is contradictory and cannot therefore be considered of sufficiently high standard to satisfactorily demonstrate efficacy.

The sponsor has potentially introduced bias by describing missing subjects in the placebo arm as treatment failures. The conservative view would consider missing data in placebo subjects as treatment successes, and missing data in the Hemangiol arm as treatment failures. The effect of this bias is to overestimate the treatment effect.

3. Effect of study site

The Guideline for a single pivotal study has a pre-requisite that 'None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect'. No assessment of the effect of study centre was undertaken, therefore has not been satisfactorily established.

4. Long-term follow-up

It is a prerequisite of paediatric studies to have adequate long-term follow-up. No efficacy data was submitted for evaluation from the Week 72 post-treatment assessment point which was a secondary efficacy outcome.

5. Validity of assessment tool and diagnostic bias

A diagnostic test should be validated in at least two separate populations for the validity of the test to be established, reporting the sensitivity and specificity of the test. The use of photography to diagnose treatment efficacy of Hemangiol was not established in a separate population outside of the pivotal study; it is therefore not satisfactorily demonstrated that the assessment test is valid[51].

The validity and clinical relevance of the description 'nearly complete resolution' has not been satisfactorily demonstrated. The sponsor has not satisfactorily demonstrated that the observed perceived outcome of 'nearly completely resolved' is unequivocally representative of the final outcome 'completely resolved'. The final outcomes for the proportion assigned 'nearly completely resolved' needs to be compared to the absolute final outcome (beyond Week 24) of 'completely resolved', specifically reporting the scarring and skin colour changes between these time-points. Given that the sponsor has not recorded, nor reported, these two outcome categories separately for the primary analysis, the validity of the designation of 'nearly complete resolution' status to categorically reflect later 'complete resolution' status is uncertain.

The assessment method allowed a lesion to be categorised as a 'success' following treatment with too broad a range of outcomes. An IH with complete resolution, and no sequelae, is considered the same as an IH with complete resolution and marked sequelae: the Delegate considers that this does not represent the same clinical outcome.

[51] Haynes R. et al. Clinical Epidemiology – How to do clinical practice research. 2006 3rd Edition. ISBN-13:978-07817-4524-6

The method used by the central observers of using photographs to describe the 'success' of treatment is non-specific, subjective and not reproducible among observers that have not received the 'specific training' by the sponsor. The Delegate agrees with the clinical evaluator that the sponsor has not adequately validated the assessment method used by the blinded assessors in the pivotal study, resulting in a lack of external validity and generalisability. The 'specific training' given to the blinded observers was not described and therefore cannot be reproduced.

Treatment 'success' was determined by four separate and distinct outcome possibilities. The term 'nearly-completely resolved' is not reproducibly defined by any specific biological characteristic of the IH lesion, and is only further described using subjective terms of 'minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks'. The natural history of an IH is for all lesions to completely resolve, with or without varying degrees of: scarring, telangiectasis or skin discolouration. The sponsor has not collected the data for those that achieved a 'complete response' separately from those that achieved a 'nearly-complete' response, which precludes a meaningful assessment of the treatment effect over time. By definition, a lesion that has 'nearly-completely resolved' has incomplete resolution, and is thus only a surrogate for complete resolution. Given that the composite outcome of treatment 'success' includes a surrogate, the method is not sufficient rigorous for regulatory purposes to adequately determine the true effect of treatment.

What constitutes a 'minimal degree' of each of the components of the assessment is not adequately defined to be reproducible. The natural history of the five individual component items assessed by the blinded observers has not been reported.

Specific inadequacies of the assessment method are:

Soft tissue swelling and tenseness: For the blinded assessors, the sponsor has described the 'definition' of tenseness as 'considered present when the superficial component was shiny (from camera flash reflectance) with a bright red hue' (sponsor's response to the TGA request for information). This description does not represent a reliable or reproducible measurement. The sponsor has made the assumption that skin reflectance is a binary outcome dependent upon the tenseness of the lesion. This method is not substantiated: no validation of the reflectivity of the skin, as assessed by camera flash reflectance was made against a validated and standardised measurement of skin reflectance nor was it correlated with an IH pressure measurement. Furthermore, skin reflectance is dependent upon a number of other factors which also change over time with the development of the skin of an infant, for example, dermal thickness, melanocyte count and degree of pigmentation, which may minimise skin reflectance over time independently from a change in the IH[52, 53]. Therefore a lack of reflectivity of a camera flash cannot be solely ascribed to a change in the hemangioma. The descriptor of 'a red hue' is not defined and is unreproducible.

Soft tissue swelling is not solely a feature of the lesion, but may also be affected by total-body hydration. It therefore cannot be solely ascribed to a change in the hemangioma itself. This element of the assessment is not sufficiently reliable for regulatory purposes.

Skin thickening: The photographic assessment of treatment effect required an evaluation of 'skin thickening'. Skin thickness cannot be assessed using a photograph. Therefore this element of the assessment method is critically flawed. Since no skin thickness measurements were taken, this element of the assessment is not sufficiently reliable for regulatory purposes.

Distortion of anatomical landmarks: The definition of a minimal degree of distortion of anatomical landmarks has not been given. Adequate assessment of a change in distortion of

[52] Lister, T. Wright, P. Chappell, P. Optical properties of human skin. *J Biomed Optics* 2012:17(9); 090901-1 to 090901-15.
[53] Jacques, S. Optical properties of biological tissues: a review. *Physics in Medicine and Biology*. 2013: 58: R37-R61

an anatomical landmark over time requires a categorical or continuous scale of measurement, rather than a subjective assessment. This element of the assessment is not sufficiently reliable for regulatory purposes.

6. Differential misclassification bias

The primary efficacy outcome of the pivotal trial, the assessment of complete or nearly complete resolution at Week 24 compared to baseline using the ITT population, is invalid (1) due to the use of an inadequately validated primary outcome of nearly complete resolution, and (2) due to the high proportion of the placebo arm (65.5%) that prematurely discontinued treatment prior to that assessment point. In randomised controlled trials that have a high and differential drop out between treatment arms, the ITT analysis overestimates the treatment effect if the loss to follow-up is in the placebo arm[54]. The reported per-protocol assessment is not valid for this study as there were a significant proportion of the placebo group that crossed-over to prohibited treatment(s), yet were erroneously included in the final analysis.

7. Blinded and non-blinded observation

A consistent treatment effect has not been demonstrated by the blinded and non-blinded assessors despite them using an almost identical method of assessment. Were the treatment effect of Hemangiol of such a demonstrable benefit, it would be expected that both groups of assessors would have reached a similar conclusion. The blinded and on-site assessors used the same method to assess treatment effect, with the exception that the on-site assessors also reported the lesion palpable component. There are insufficient differences between the two methods to dismiss the on-site assessment method and both have to be considered valid.

Given the limitations of the blinded observers to determine soft-tissue swelling and tenseness and skin thickness from photography, as described above, the Delegate considers that these limitations are not problematic for real-time on-site examinations. The Delegate considers the on-site assessments to be a better reflection of routine clinical practice, and thus more consistent with the likely treatment effect.

Given that there are equivocal results from the two groups of assessors, the Delegate is required to take the conservative view of the treatment effect, that is, that of the on-site observers, which demonstrated no benefit of Hemangiol over placebo.

Given that no treatment effect has been shown by on-site observers, this precludes the pivotal study to demonstrate 'exceptionally compelling' evidence of Hemangiol efficacy, as is required by the relevant Guideline.

There is a discrepancy between the proposed indication of including patients 'requiring systemic therapy' and those who actually achieved a benefit from it, given only 27% of the Hemangiol arm assessed by on-site evaluators had a reported 'success'.

8. Inadequate assessment of placebo group

There is inadequate follow-up of those patients that left the study early. Only 14 out of 36 (39%) of subjects in the placebo arm were subsequently assessed following premature exit from the study. Indeed, the sponsor concedes in the sponsor's response to the TGA request for information: 'this makes it impossible to evaluate the spontaneous regression when stopping the placebo treatment'. Due to cross-over to active treatment, and lack of follow-up of the placebo group, the Delegate considers it impossible to satisfactorily compare the outcome between the placebo and propranolol arms.

9. Length-biased sampling

The primary efficacy assessment point of 24 weeks is arbitrarily set. Given that all IH eventually spontaneously regress, it is entirely plausible that an earlier, or later, assessment

[54] Hernan, M. Hernandez-Diaz, S. Beyond the intention-to-treat in comparative effectiveness research. *Clinical Trials* 2012:9;48-55.

time-point may yield a different proportion of subjects, in each treatment arm, with complete regression. Indeed, it would be anticipated that a longer time to assessment would eventually yield no difference in the proportions achieving complete regression. There is no cogent argument for accepting this 24 Week time–point as opposed to any other, and its clinical relevance is not established by this submission.

The time-point where an individual lesion is completely resolved, with or without sequelae, is the absolute measure of efficacy. The lesion status of 'nearly complete resolution' is only a surrogate for the actual end-point of 'complete resolution'. For each IH, the time to complete resolution is dependent upon three time periods: the pre-treatment period, treatment period and post-treatment period. The primary efficacy end-point is potentially biased due to stratification factor used which was the age of the child rather than stratification according to the pre-treatment duration of the lesion. The age of the child is independent of the age of the lesion. Given the postulated mechanism of action of propranolol in proliferating hemangioma, it is entirely plausible that subjects with lesions that were randomised nearing the end of the proliferative phase would be less responsive than those at the beginning of it, but this effect cannot be determined from the pivotal study. Indeed the sponsor (in the response to second round CER) states: there is an emerging consensus for an early initiation of treatment'; however, this statement cannot be justified by the evidence form the pivotal trial, given the randomisation method.

Furthermore, it cannot be established from the pivotal trial if there is a critical or sensitive period for propranolol to be efficacious or not. The sponsor has not satisfactorily provided evidence of the length of the post-treatment period for 'nearly completely resolved' lesions to achieve 'complete resolution' status. Indeed the total duration of the lesions has neither been demonstrated to be different between the treatment arms, nor does a shorter duration to complete resolution lead to a clinical improvement in the final, objective, adverse outcomes of scarring requiring intervention or skin discolouration.

10. Inclusion and exclusion biases

The pivotal study enrolled patients that 'required systemic therapy' according to the table in the efficacy section. However, the individual specific reason for requiring systemic therapy was neither collected nor reported which results in uncertainty of the initial decision to enrol.

One reason for 'the need for systemic therapy' was that a lesion was in a particular location that 'frequently causes scarring'. The sponsor has neither reported how this baseline risk is calculated nor was the observed outcome of scarring in patients in whom scarring was expected to occur frequently reported. Given the lack of adequate pre-treatment risk assessment, the use of Hemangiol for this subgroup of patients has not been satisfactorily established.

In the pivotal trial, infants that had either a function-threatening or an ulcerated lesion at the time of recruitment should have excluded. Seven patients had lesions that progressed to cause functional impairment during the course of the study. By definition, the IH in these patients had the potential to be function-threatening from the outset, and consequently they should have been withdrawn from the study as they met the exclusion criterion.

11. Inadequate description of non-responders

In subjects that did not achieve a treatment response to Hemangiol, none subsequently had a histologically confirmed diagnosis. Other types of vascular malformations may mimic IH such as hemangioendothelioma, and may be equally non-responsive to beta-blocker but may be to other agents, such as vincristine. Given the lack of confirmatory histology and data on subsequent treatments for these subjects, it is uncertain if non-responders in the propranolol arm truly had IH, which is a source of ascertainment bias.

12. Relapse following cessation of treatment and continued efficacy

The sponsor quoted a 5-25% relapse rate following cessation of propranolol treatment in the SCS. However the proportion of patients treated with Hemangiol who relapsed in the pivotal study has neither been reported, nor are the subsequent treatments required for these subjects described. There is insufficient data to demonstrate continued efficacy, or lack thereof, beyond the 24 Week double blind treatment period[55].

Efficacy: supportive studies

Efficacy was not prospectively assessed in the subjects with high-risk IH enrolled into the CUP. The efficacy data presented from the CUP is not sufficiently robust for regulatory purposes to satisfactorily demonstrate a benefit from Hemangiol use in high-risk IH lesions, and to recommend Marketing Authorisation. There is missing data for 66% of all evaluable subjects that received Hemangiol treatment.

Only 7.7% of subjects received the proposed dose of 3 mg/kg/day. These subjects had an inadequate assessment of efficacy. There is no update of safety presented with the update of 'efficacy' included in the response to second round TGA evaluations.

There is extremely limited efficacy data from the dose finding Study 102. The reported outcomes of 22/23 un-randomised subjects with high-risk lesions is insufficient to satisfactorily extrapolate Hemangiol use into a wider population. Furthermore, the dose used in this study was 3 mg/kg/day, which has not been supported by the pivotal trial due to comparison of efficacy with an inadequate placebo group.

Other: Consensus statement

Hemangiol should be contraindicated in infants less than 2.5 kg given the potential for measurement error of dosing, and inadvertent overdose using the sponsor-supplied syringe. The indication for Hemangiol includes a post-term corrected age limit of 5 weeks. The lower bound of the 97% confidence interval for weight for this age is approximately 3.7 kg. It would unusual for an Australian child to be discharged from hospital with a current weight of 2.5 kg at 5 weeks of age without a reason for their severe growth restriction being ascertained. Setting a weight limit of 2.5 kg is unlikely to cause disadvantage.

There is only one published consensus statement regarding the use of propranolol for the treatment of infantile hemangioma[56]. This statement is potentially biased as a number of the authors have a conflict of interest due to involvement with the sponsor of Hemangiol. This notwithstanding, the advice contained includes:

- 'A formulation of 20 mg/5 mL is used'
- 'The dose of propranolol be divided into 3 times daily.'

The formulation of Hemangiol and proposed dosing frequency is different to that proposed by this consensus statement.

Deficiencies with the submission

At the pre-submission planning stage of the application the sponsor did not request a literature based submission evaluation. The sponsor has included a large number of self-selected publications, of predominately observational and non-randomised studies, in the evaluation and post-evaluation phases. These publications are noted by the Delegate but are insufficient to support registration of Hemangiol in the proposed indication given:

[55] Drolet et al. Initiation and use of propranolol for infantile hemangioma: report of a Consensus Conference. *Pediatrics* 2012:131(1);128-140.
[56] Bagazgoitia, L. Hernandez-Martin, A. Torrelo, A. Recurrence of infantile hemangiomas treated with propranolol. *Pediatric Dermatology* 2011:28(2);658-662.

- they do not conform to the TGA process of an pre-submission, mutually agreed search strategy; consequently there is a risk of bias from only favourable studies being presented;
- the dose, and frequency of administration of propranolol used is not standardised to that proposed by the sponsor, limiting the comparison of safety and efficacy;
- the formulation of propranolol used is not solely Hemangiol; and
- the management and reporting of AEs is not standardised with those proposed by the sponsor.

The sponsor has included a number of post-hoc analyses in the sponsor's response to the TGA request for information and in the response to the second round CER. These analyses cannot be used as they are speculative in nature.

The sponsor provided RMP documents for evaluation in the post-evaluation phase of the submission process, up to the day before the completion of the Delegate's Overview. This has not allowed the Delegate sufficient time to consider these documents and contribute to the decision regarding Marketing Authorisation.

The sponsor has not provided a study on the child-safety standard for the proposed Hemangiol container, despite stating that it would be available prior to the cutoff for completion of the Overview.

Proposed action Decision

The safety of Hemangiol in the sponsor-proposed indication has not been satisfactorily established given that, in the pivotal study:

1. Outcomes for subjects that crossed over from placebo to active treatment are included in the placebo safety set, leading to uncertainty of the incidence of AEs
2. There is significant loss to follow-up of the placebo group leading to uncertainty of the incidence of AEs
3. The risk of adverse neurocognitive development, in otherwise healthy subjects with low-risk lesions, was neither assessed nor reported
4. There is a reported greater risk of IH ulceration, and consequently scarring of lesions, following active treatment for subjects in the pivotal study
5. The risks of hypoglycaemia, and/or seizures are unacceptable in otherwise healthy patients with low-risk lesions that have a natural tendency to regress spontaneously

The efficacy of Hemangiol in the sponsor-proposed indication has not been satisfactorily established given significant flaws in methodology of the pivotal study of:

1. Differential loss to follow-up between treatment arms
2. Cross-over prior to the primary efficacy assessment
3. Lack of validation of the assessment method
4. Substantial divergence of opinion of the blinded and on-site observers, using a very similar assessment method
5. Numerous sources of potential bias and consequent lack of external validity of the pivotal study
6. Lack of data presented to support that a sustained treatment effect beyond Week 24 following cessation of treatment

7. Lack of evidence presented to satisfactorily demonstrate a definition as to which low-risk IH lesions actually 'require systemic therapy'
8. Given a lack of satisfactory definition as to which lesions 'require systemic therapy', approval for this indication could potentially include all lesions, thereby exceeding the prevalence limit for the Orphan Drug designation

The dose of Hemangiol chosen as the 'best' in the pivotal study (3 mg/kg/day) was made in comparison with a placebo group in which the majority of subjects had not been formally assessed at the primary efficacy time point.

The efficacy of Hemangiol was not prospectively evaluated in the subjects treated in the CUP. The majority of infants (92%) received a Hemangiol regimen different to the 3 mg/kg/day regimen proposed by the sponsor. There is substantial missing data which precludes the generalisation of treatment from this group of patients to a wider population.

The efficacy of Hemangiol in Study 102 was only reported in 22 subjects. The outcomes from this cohort have not been reported separately, which precludes the meaningful assessment of efficacy and safety. No long-term safety data has been presented for these patients. Generalisation of treatment from this very small group to a wider population cannot be made with certainty. The dose regimen for these patients was 3 mg/kg/day, which is not supported by the evidence from the pivotal study.

The sponsor has not satisfactorily demonstrated that the proposed Hemangiol container meets the relevant standard for being child-resistant.

The RMP evaluation was not able to be completed at the time of writing the Overview due to the very late submission of the EU-RMP by the sponsor on the day before the Overview was due.

The Delegate does not support registration of Hemangiol for the sponsor-proposed indication of: *Treatment of proliferating infantile hemangioma requiring systemic therapy*.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and to request the committee provide advice on the following specific issues:

1. What is the opinion of the committee regarding the ability of the single pivotal study to demonstrate efficacy and safety in subjects with low-risk IH?
2. What is the opinion of the committee of the ability of the CUP and Study 102 to satisfactorily demonstrate efficacy and safety in subjects with high-risk IH?
3. What is the opinion of the committee regarding the identification of a population in which Hemangiol can be recommended for registration, and which dose should be used?

Response from Sponsor

Further to the Delegate's overview, it appears that some of the Delegate's comments and conclusions may result from the analysis of version 1 of the SAP of the pivotal study (the applicable version is version 3.3 of the SAP, dated July 20th, 2012 and transmitted to the TGA in the submission dossier), or from a misunderstanding of the data and analyses provided in the application, or from erroneous calculations. In order to address these numerous comments within the defined frame, the sponsor provides below the required clarifications while addressing the 3 points on which advice from the committee is sought. Within the provided clarifications are addressed most of the points raised in the Delegate's overview, and more specifically the issues raised under *Proposed Action: Decision*.

What is the opinion of the committee regarding the ability of the single pivotal study to demonstrate efficacy and safety in subjects with low-risk IH?

The sponsor wishes to confirm that the pivotal Phase II/III study submitted in the application adequately demonstrates the clinical efficacy and safety of propranolol in subjects with IH, based on the following arguments:

- This study was a double-blind, multicentre, randomised, controlled versus placebo, adaptive Phase II/III trial. The placebo controlled design was the only possible design, in the absence of any approved product in this indication.
- The Phase II/III adaptive design was defined *a priori* in close interaction with authorities; the interim analysis on the planned population size was performed independently and interpreted as planned by the ICMC. There is therefore no bias associated with this interim analysis, as documented in Study 201 CSR.
- Given the lack of guidelines and validated assessments tools for the measurement of IH improvement/resolution, the primary criterion defined *a priori* in close collaboration with agencies was based on an objective, centralised analysis of standardised photographs, with on line quality assessment of the photographs, and interpretation by two blinded independent readers, using an *a priori* defined imaging charter. All precautions were taken in order to ensure reader training and consistency, both initially and during the course of the study, as described in Study 201 CSR.
- There is no bias associated to 'cross-over' to another treatment during the course of the study: all IH treatments other than the test drugs were forbidden by protocol. The possibility for participants to stop test drug before planned main efficacy visit (Week 24) if their medical situation required it (mostly for insufficient efficacy or for AEs) represented however a mandatory ethical and medical precaution: interruption of study treatment was accepted, so that the patient may receive any treatment deemed appropriate to his/her specific situation without generating any bias in the safety/efficacy assessments. Such patients were not lost to follow-up, and are taken into account in the various patient populations as defined in the SAP. For this submission dossier, only data up to Week 24 or premature EOT visit were analysed. Premature EOT patients were logically and prospectively defined as failures whatever the treatment group; this imputation approach is usual in such designs with binary endpoints. Therefore, primary endpoint was available on the full study population. The percentage of patients whose treatment was not maintained until Week 24 was higher in the placebo group (65.5%), and most of the cases were linked to insufficient efficacy (89% of interruptions); considering these cases as failure is therefore a legitimate approach. Fewer patients on propranolol had early treatment interruption (13.7% in the 3 mg/kg/day 6 months group). Considering these cases as failures, irrespective of the evolution of IH, is therefore a very conservative approach. Therefore, the primary efficacy analysis (based on the ITT approach) is not biased due to different rates of early treatment discontinuations.
- The actual rate of patients lost to follow-up is therefore low, and does not differ between groups. A total of 11 patients out of 460 were lost to follow-up (1 on placebo (1.8%): 2 each in the 3 months arms (2.0%) and 3 each in the 6 months arms (2.9%)). There is therefore no bias attributable to patients lost to follow-up, either for efficacy or for safety analyses.
- The primary efficacy assessment analysis demonstrates the efficacy of the dose and treatment duration selected, in comparison with placebo. The difference in response rates is of a high magnitude, with respectively 60.4% of responders on propranolol and 3.6% on placebo. In order to take into account both the adaptive design and the single Phase III study, the Type I error rate had to be below the nominal one-sided significance level of 0.005. The statistical significance of the primary efficacy analysis provides a p <

0.0001, meeting therefore this requirement. The study meets therefore criteria for a positive demonstration.

- Several sensitivity analyses were performed to assess the robustness of the primary analysis; one sensitivity analysis with relaxation of the definition of failures in case of premature EOT confirmed the results of the primary analysis (significant superiority of the active treatment regimen) despite the high artificial increase of the success rate in the placebo regimen (27.3% on placebo versus 61.4% on propranolol). Two additional sensitivity analyses confirm the robustness of the primary analysis: one on the patients having completed the treatment period (10.5% versus 69.3%) and one with a new handling of early discontinuations using multiple imputation method (13.8% versus 67.9%). In conclusion, all planned and post-hoc sensitivity analyses do confirm the results of the primary analysis and the absence of any bias generated by the definition of early treatment withdrawals as failures.
- The difference between the primary efficacy criterion (success as defined by the centralised readers on photographs) and one single secondary criterion (success as defined by the investigator but with significative methodologic differences that prevent to compare them) and their corresponding results is discussed in the CSR. Such a difference between results does not in itself cast doubt as to the validity of the primary criterion; as a matter of fact, several secondary criteria (first sustained improvement as assessed by central readers, by investigators and by parents) also provide strong and statistically significant demonstration of efficacy (CSR 201).
- The sustainability of effect can be estimated through the long-term, off treatment, follow-up period of the Phase II/III study (analysis recently completed not submitted in the current registration dossier, available upon request), where patients were re-assessed for IH 12, 24, 36 and 72 weeks after Week 24. Out of 54 patients from the 3 mg/kg/day 6 months arm achieving success at Week 24 (primary endpoint) who entered the follow-up period, and with success assessment available at Week 96, 35 (64.8%) achieved success at Week 96 without any additional treatment for their IH over the follow-up period (that is, sustained response). Out of the 61 patients from the 3 mg/kg/day 6-month arm with success at Week 24 (primary endpoint) and who entered the follow-up period, only 7 (11.5%) required re-initiation of IH treatment over the Week 24-Week 96 follow-up period, confirming that the successful results obtained at Week 24 were sustained after treatment discontinuation.

The analysis of safety data in the pivotal study was done with the most appropriate approach, taking into account all AEs during the actual test drug intake period, with an extension up to 5 days after treatment interruption in order to make sure that no AE is omitted. This approach also ensured that no bias could be due to possible events due to subsequent treatments. Therefore, there is no overestimate of the rate of AEs on placebo, and all comparisons provided in the submission are valid and reliable, all percentages being provided on actual populations, and should be interpreted in relation with exposure, which is lower for placebo.

The Delegate evokes a 'higher risk of IH ulceration', whereas the rate of complications of IH, and especially of ulcerations, was in no case higher on propranolol (3.9%) than on placebo (3.6%), percentages being almost identical, and in both cases very low. There is therefore no signal on this point. In order to ensure adequate detection and safe management of potential hypoglycaemia cases, patients had their blood glucose measured on three occasions on each up-titration day (time 0, 2 h and 4 h). Only 2 cases of asymptomatic hypoglycaemia were reported as AE on treatment, both during the up-titration period (1 patient at 1 mg/kg/day and 1 patient at 3 mg/kg/day) and none was reported at Week 12 and Week 24. Only 1 case of hypoglycaemia was < 2.5 mmol/L (2.3 mmol/L on Day 7 on a dose of 1 mg/kg/day).

Neurocognitive development was systematically assessed in all patients attending the Week 96 visit; based on the recently completed analysis of this period, 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 small numbers and the overlap of the CIs do 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 slightly 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. A specific safety study performed in juvenile animals showed no test item treatment related effects or toxicologically significant findings in terms of reproductive development, growth or neurological development. Two studies recently presented at the International Society for the Study of Vascular Anomalies (ISSVA) meeting held in Melbourne (April 2014), showed the absence of any developmental defect over respectively 12 months and 4 years of follow-up in children whose IH was treated with propranolol. Taken all together, these data provide reassurance as to the lack of deleterious effect of propranolol on the development of infants.

In conclusion, the pivotal study met its objective, with a statistical and clinical demonstration of the efficacy of propranolol in the treatment of IH in comparison with placebo, the demonstration of the optimal dose regimen (3 mg/kg/day for 6 months) and adequate documentation of the safety profile, without any unexpected safety signal.

What is the opinion of the committee of the ability of the CUP and Study 102 to satisfactorily demonstrate efficacy and safety in subjects with high-risk IH?

IH requiring systemic therapy can be separated in 2 subgroups:

- High-risk IH
- Non high-risk IH but still requiring systemic therapy (so called 'low-risk IH' by the Delegate, creating a confusion because they are severe IH)

High-risk IH are impossible to include in a randomised placebo controlled trial for ethical reasons. Thus, only non high-risk IH but still requiring systemic therapy were included in the pivotal 201 Phase II/III study.

There was an agreement with FDA that this restriction would not preclude approval in subjects with more severe lesions and this was later confirmed by the approvals granted by FDA and EMA in both populations.

Moreover, considering the poor benefit/risk ratio of corticosteroids in IH (not approved in US, Australia and most EU countries), FDA and EMA have also considered unethical to include a corticosteroid arm in the pivotal 201 Phase II/III study.

Therefore, even a study in high-risk IH comparing propranolol with corticosteroids is not feasible and this was also further demonstrated by the early interruption of the recent study of Bauman[57], with 6 interruptions of treatment for safety reason on the 8 children in the corticosteroid arm (versus 0 in the propranolol arm).

In conclusion, based on a pragmatic approach in this unique situation, both FDA and EMA agreed to support the indication in high-risk IH based on:

[57] Bauman NM et al. Propranolol vs Prednisolone for Symptomatic Proliferating Infantile Hemangiomas A Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg*. doi:10.1001/jamaoto.2013.6723. Published on-line 13 February 2014.

1. *Compassionate Use program*: Data from the CUP, on a large population of patients (more than 900 patients) who all had high-risk IH, provide reassurance on the efficacy of Hemangiol in the target population. In the CUP, efficacy was estimated through evaluation of reasons for treatment discontinuation. Analysis of cumulative CUP data up to the cutoff date of 12 April 2013 showed that, of the 313 patients in whom treatment discontinuation is documented, 262 (83,7%) did so due to good efficacy, and that 58.1% of the patients whose response was further detailed, had complete or nearly complete resolution of their IH. The sponsor confirms that a significant proportion of patients (21.9%, and not 8% as calculated by the Delegate) received at least one dose of 3 mg/kg/day.
2. *Study 102*: In this open label Study 102, patients (n = 7) with high-risk IH received propranolol, with resolution of all complications in all cases.
3. *Extrapolation* to the high-risk IH of the results of the pivotal 201 Phase II/III study, in the absence of pathophysiological difference related to the severity or risk of IH. The properties of propranolol that support the demonstration of its efficacy in Study 201, should therefore apply to other forms of IH, including high-risk IH. Supporting this point, success rates in study 201 were comparable between facial and non-facial IH and between the overall population and a subpopulation with higher-risk IH.
4. *Literature analysis*: An extensive literature search identified a large number of publications that reported cases, case series or studies of patients with various forms of high-risk IH, including ocular IH, airways IH, hepatic IH and PHACEs. All publications reported a significant improvement of IH lesions and of the functional complications but these data were apparently not taken into consideration by the Delegate.

In conclusion, the approach used in this submission is the only possible way to demonstrate the efficacy/safety of propranolol in IH and to support its use in high-risk IH in which the benefit risk ratio is the most favourable.

What is the opinion of the committee regarding the identification of a population in which Hemangiol can be recommended for registration, and which dose should be used?

As documented in the sponsor's 'Response to the second round comments and errors of fact/omission from the clinical evaluation' on April 10th, 2014, the target population in which Hemangiol is submitted is infants with IH requiring systemic therapy, defined as

i. life/function threatening IH,

ii. ulcerated IH with pain and/or lack of response to simple wound care measures, and

iii. IH with a risk of permanent scars or disfigurement.

The selection of the 3 mg/kg/day for 6 months is justified on the following arguments:

The efficacy results in Study SB 201 obtained at 3 mg/kg/day for 6 months show a high level of efficacy: 60.4% of complete/nearly complete resolution, 88.0% of improvement at W5 versus baseline, 72.7% of sustained improvement since Week 5. The dose of 1 mg/kg/day for 6 months, while showing some efficacy, permits a complete/nearly complete resolution in some 11% fewer patients. Since the safety of the 3 mg/kg/day dose is documented as satisfactory, it seems therefore justified to retain the 3 mg/kg/day for 6 months. When treating IH patients for 6 months at the 3 mg/kg/day dose, 11.5% of them needed to be re-treated when discontinuing treatment. This means that in 88.5% of cases, a 6 month duration was sufficient to treat IH, without the need for any extended or repeated treatment.

The dose of 3 mg/kg/day for 6 months is therefore demonstrated as bringing significant efficacy with a low rate of relapse after treatment cessation.

Delegate's recommendations for the Product Information

The sponsor agrees with all the Delegate's recommendations for the product information which were included in the updated PI except ones concerning sections *Indications*, *Precautions* and *Adverse events*:

Indications and Precautions: The Delegate does not support the indication claimed by the sponsor: *'Treatment of proliferating infantile hemangioma requiring systemic therapy'* and proposes that the information in the *Precautions* section becomes the indication.

The sponsor has decided to keep the section *Precautions* as it is but to amend the indication in order to make it more specific:

Treatment of proliferating IH requiring systemic therapy:

- *Life-threatening hemangioma*
- *Ulcerated hemangioma with pain and/or lack of response to simple wound care measures*
- *Hemangiomas with a risk of permanent scars or disfigurement.*

It has to be noted that this indication is the one approved by the EMA.

Adverse events:

Details are beyond the scope of the AusPAR.

Clarification on the literature and study report submitted

The sponsor would like to insist on the fact that its marketing authorisation request for Hemangiol is based on clinical trials studies including Phase II/III study but is also supported by literature for nonclinical and clinical parts

Moreover, the sponsor would like to underline that the study report regarding the child-resistance of the container study is available and has been submitted to the TGA. It has to be noted that the study concluded that the primary packaging complies with the requirements of the Protocol US 16 CFR §1700.20 and that the child resistant system of the closure is maintained after simulated use.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Hemangiol oral solution containing 3.75 mg/mL of propranolol hydrochloride has an overall negative benefit-risk profile because of a lack of robust, valid and reliable data on safety and efficacy for the proposed indication.

Specific advice:

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. What is the opinion of the committee regarding the ability of the single pivotal study to demonstrate efficacy and safety in subjects with low-risk IH?

ACPM considered the methodological flaws in the pivotal efficacy and safety study prevented valid, reliable conclusions to be made regarding the efficacy and safety of oral propranolol in subjects with low-risk IH.

The ACPM was of the view that there was no clinical rationale for the routine treatment of low-risk IH in Australia and that current practice is to treat (with compounded propranolol) infants with high-risk IH only.

2. What is the opinion of the Committee of the ability of the CUP and Study 102 to satisfactorily demonstrate efficacy and safety in subjects with high-risk IH?

Members considered that data from Study 102 and from the CUP, as well as much of the data from the submitted literature, were observational and did not allow valid, reliable conclusions to be made regarding the efficacy of Hemangiol in high-risk IH.

3. What is the opinion of the Committee regarding the identification of a population in which Hemangiol can be recommended for registration, and which dose should be used?

The ACPM considered the submission did not include scientifically robust, valid and reliable data to justify the approval of Hemangiol for the treatment of IH of any severity.

Initial decision

The TGA reviewed the quality, safety and efficacy data submitted in support of the application to register Hemangiol (propranolol hydrochloride) oral solution for the following indication:

Treatment of proliferating hemangioma requiring systemic therapy

Pursuant to section 25 of the Therapeutic Goods Act 1989 ('the Act') the Delegate of the Secretary notified the sponsor of the **decision not to register Hemangiol (propranolol) oral solution** in the treatment of proliferating hemangioma requiring systemic therapy on the grounds that the efficacy and safety of the product have not been satisfactorily established for the purposed for which it is to be used.

Reasons for decision

The safety of Hemangiol (propranolol hydrochloride) in the indication *'treatment of proliferating infantile hemangioma requiring systemic therapy'* has not been satisfactorily established for the following reasons:

- In Study 201, the incidence of AEs due to Hemangiol exposure cannot be satisfactorily determined due to the method of reporting AEs only according to the initial treatment assignation. This method of reporting underestimates the true incidence of AEs given that 65% of the placebo arm patients were also treated with Hemangiol.
- The sponsor defined hypoglycaemia requiring treatment as a level of 2.2 mmol/L, which is lower than the accepted Australian definition of hypoglycaemia in infants of 2.6 mmol/L.
- The risk of hypoglycaemia was demonstrated to occur beyond the initial titration phase in Hemangiol-exposed infants in the pivotal study.
- No advice on routine blood glucose monitoring is contained in the PI. Despite the observed AEs of symptomatic and asymptomatic hypoglycaemia, the sponsor has not provided a satisfactory explanation as to why routine blood glucose monitoring is not recommended during Hemangiol exposure.
- The incidence of AEs in the 922 patients exposed to Hemangiol in the CUP cannot be satisfactorily determined. In the response to the Delegate's overview, the sponsor states 'the true incidence of ADRs collected during the CUP is underestimated and therefore

should not be used as reference in the product information'. This does not represent a satisfactory pharmacovigilance activity to permit registration of Hemangiol.

- Given the lack of safety data from the CUP, in the response to the Delegate's overview, the sponsor requested that the PI report the frequency of AEs of: hypoglycaemic seizure, bradycardia, hypotension, vasoconstriction, Raynaud's phenomenon, agranulocytosis and hyperkalaemia with the phrase 'not known'. This demonstrates an inadequate characterisation of the safety profile of Hemangiol and the Delegate cannot approve the PI using this uncertain, and unsafe, terminology.
- Despite the paucity of safety data from the CUP, the proposed PI states: 'The most severe risks reported in the CUP and in the literature concerned hypoglycaemia (and related events such as hypoglycaemic seizure)'. The risks of these events are inadequately described to satisfactorily inform the prescriber of the risks of Hemangiol use, given that the sponsor acknowledges the true incidence of events is underestimated in this population.
- Given there is uncertainty regarding the incidence of AEs in study 201, the reported AE profile in this study cannot be assumed to be the same for those treated in the CUP.
- The risk of adverse neurodevelopmental development following Hemangiol exposure cannot be satisfactorily established given the paucity of safety data from the CUP and the reporting method from Study 201. Neurodevelopmental outcome has only been reported for 322 of the 922 (35%) patients in the CUP, therefore the true incidence of adverse neurodevelopmental outcome has not been satisfactorily established for this cohort.
- Given the reporting method from Study 201, where outcomes were described according to the treatment the patient was initially randomised to as opposed to whether they received Hemangiol treatment, and the lack of safety data from the CUP, both the denominator of patients exposed to Hemangiol is uncertain and the true incidence of any AEs is not ascertainable.

The efficacy of Hemangiol (propranolol) in the indication *'treatment of proliferating infantile hemangioma requiring systemic therapy'* has not been satisfactorily established for the following reasons:

- Study 201 permitted patients to cross from one treatment arm to the other prior to the primary efficacy assessment point, breaking the randomisation strategy employed, which yields uncertainty of the efficacy outcome.
- The choice of the proposed regimen of Hemangiol, from the four possible in Study 201, is uncertain as it was selected against a placebo arm in which only 24% of the 35 required patients in the placebo arm had completed treatment to Week 24, the primary efficacy assessment point.
- In regard to patients exchanging treatments prior to the primary efficacy assessment, the sponsor states: 'It is impossible to predict exactly what the outcomes at Week 24 would have been had these patients continued to receive the assigned study treatment'.
- A consistent treatment effect of Hemangiol was not demonstrated between central and on-site assessors, despite using the same assessment method; with the exception that the on-site assessors could describe the physical findings of their patient examinations. This finding is contrary to the requirement of a single pivotal study to demonstrate 'exceptionally compelling evidence' of efficacy.
- The central assessors were given 'special training' to be able to evaluate the outcomes. The 'special training' is not described by the sponsor and is therefore not reproducible.
- The method of assessment of photographs used by the blinded assessors was not validated in a separate population prior to use in the pivotal study.

- It is uncertain that the blinded observers could satisfactorily assess soft tissue swelling and skin turgor using lesion photographs alone, yielding uncertainty of the validity of the blinded assessment method.
- The categorisation of treatment 'success' includes clinically diverse outcomes ranging from 'complete resolution with no sequelae' to 'complete resolution with marked sequelae', which are of unequal clinical significance.
- Additional treatments required by those subjects with 'complete resolution with marked sequelae' have not been described.
- The sponsor has not satisfactorily defined the term 'need for systemic therapy' of infantile hemangioma.
- The sponsor has not satisfactorily described the outcomes, and additional treatments required by infants who did not respond to Hemangiol therapy.
- The sponsor has not satisfactorily described the outcomes for patients that relapsed following cessation of Hemangiol therapy, or any additional treatments required.

Following receipt of the Delegates overview, the sponsor changed the proposed indication to:

> *Treatment of proliferating IH requiring systemic therapy:*
>
> - *Life-threatening hemangioma*
> - *Ulcerated hemangioma with pain and/or lack of response to simple wound care measures*
> - *Hemangiomas with a risk of permanent scars or disfiguration*

The pivotal study (201) specifically excluded patients with 'high-risk' lesions therefore safety and efficacy have not been satisfactorily demonstrated for this patient group by this study. Given the pivotal study deficiencies that prevent the satisfactory demonstration of safety and efficacy in the initially proposed indication as described above, the same deficiencies also preclude the satisfactory extrapolation of this safety and efficacy data to the population in the amended indication.

In the sponsors' response to the second round evaluation reports, it states 'The CUP did not feature any prospective assessment of efficacy; therefore, efficacy could be indirectly estimated through the documentation of reasons for treatment interruption, systematically requested for all patients'. Thus, only surrogate efficacy outcomes are presented, which are not sufficiently rigorous, or validated, to satisfactorily establish efficacy in the 'high-risk' patients treated with Hemangiol.

Efficacy outcomes from the CUP are not reported for 609/922 (66%) subjects treated with Hemangiol. Therefore efficacy has not been satisfactorily demonstrated for this entire group of patients.

The sponsor has neither satisfactorily demonstrated how the pre-treatment assessment of 'risk of scarring or disfiguration' is determined nor satisfactorily described the outcomes of scarring or disfigurement in the 'high-risk' patients treated with Hemangiol.

The efficacy and safety of Hemangiol in the treatment of 'high-risk' lesions has not been satisfactorily demonstrated by the evidence in the submission, due to the specific exclusion of such patients from the pivotal study and the paucity of efficacy and safety data presented from the CUP. Furthermore, the ACPM advised that 'data from Study 102 and from the CUP, as well as much of the data from the submitted literature, were observational and did not allow valid, reliable conclusions to be made regarding the efficacy of Hemangiol in high-risk IH'.

The Delegate considers that the evidence provided in the submission does not support registration of Hemangiol in the initially proposed indication. This opinion was supported by

the advice of the ACPM that 'Hemangiol oral solution containing 3.75 mg/mL of propranolol hydrochloride has an overall negative risk-benefit profile because of a lack of robust, valid and reliable data on safety and efficacy for the proposed indication.'

The Delegate considers that the evidence provided in the submission does not support registration of Hemangiol for the treatment of infantile hemangioma of any severity. This opinion was supported by the advice of the ACPM that 'The ACPM considered the submission did not include scientifically robust, valid and reliable data to justify the approval of Hemangiol for the treatment of infantile hemangioma of any severity'.

The sponsor did not comply with the TGA requirements of a literature-based submission at the pre-submission planning phase of the submission of: i) prior agreement of an acceptable literature search strategy and ii) the criteria for determining which of the papers identified by the search are to be included/excluded from the submission dossier. The pre-submission planning form indicates that the sponsor would not be presenting a literature based submission.

There is no published literature provided by the sponsor pertaining to the safety or efficacy of Hemangiol as a specific formulation to support its registration.

There is no standardisation of the formulation of propranolol, or dosing regimens, in the published literature provided by the sponsor, which precludes a direct comparison with Hemangiol as a specific product in the proposed indication and in the proposed dosing regimen.

The evidence presented from the published literature does not overcome the deficiencies of the application in the satisfactory demonstration of safety and efficacy of Hemangiol in the initial and amended proposed indications.

Review of initial decision

Following the initial decision described above, the sponsor (under cover of correspondence dated 10 September 2014) sought a review of the decision under the provisions of Section 60 of the Act.

The Delegate of the Minister for the review noted that section 9A of the Act, which deals with the creation of the ARTG, and paragraph 25(1) of the Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, are of particular relevance.

Findings of fact

An application to include Hemangiol containing 3.75 mg/mL propranolol hydrochloride as an oral solution was received and accepted by the TGA. Propranolol has been used for over 60 years in adults and to a lesser extent in children.

The only outstanding issue related to chemistry and quality control is the child resistant closure, for which the company claims data have been submitted.

There are no toxicology issues outstanding.

The clinical data consisted of one pivotal study, PK studies including one with supporting efficacy data, a report from a compassionate access program and supporting literature.

The design of the pivotal study was agreed with the US FDA and EMA as being the most appropriate to investigate use of propranolol in IH. The design has some flaws as it is not possible ethically to conduct a controlled study using placebo comparator in highest risk infants, nor to deny access to active treatment for those dropping out for in efficacy but defined as requiring systemic therapy by their enrolment in the trial. The company and other

regulators have concluded there is no other ethical way to investigate use of propranolol in IH. Extrapolation of data from those requiring systemic treatment but not at risk of life or function threatening complications of IH to those with the highest risk lesions was seen as reasonable on the grounds there is no evidence that the pathophysiology of the lesions are different in these circumstances.

There are also issues with measurement of efficacy as there is no recognised validated standard and there are concerns at inconsistency in investigators assessments from published studies. For this reason the company, with the agreement of the two major regulators, designed a centralised measurement as a primary efficacy parameter. There was a discrepancy observed in the magnitude of effect between the primary efficacy measure (central reader assessment of complete/nearly complete response) and one of the secondary efficacy measures (investigator measure of complete/nearly complete response). Other secondary efficacy measures were consistent with the primary measure. Because of design issues it is possible the magnitude of the effect may be overestimated by the primary efficacy measure but there remains evidence of efficacy. The evaluator has noted that there is not an unequivocal demonstration of efficacy, but this is not required. There is consistent evidence from all the information provided that that propranolol has a beneficial effect in the treatment of infantile hemangioma.

The incidence of TEAEs is similar on the placebo and active treatment groups. However the pattern of events is different and expected AEs associated with treatment include nasopharyngitis, diarrhoea, pyrexia, bronchitis/cough. In addition, although not commonly seen, potentially more serious AEs that would be expected from the known side effect profile of propranolol include hypoglycaemia, bradycardia, hypotension and bronchospasm. The trial included risk mitigation measures to monitor and avoid these, including in-clinic monitoring of initial and up titration doses, education of parents and strict exclusion and discontinuation rules. Despite this, there were a small number of incidences of the more serious events in the pivotal trial and in the CUP. This emphasises the importance of a robust risk mitigation strategy and limiting of use to experienced specialists physicians.

Materials on which the findings of fact were based

- The submission of Pierre Fabre Australia Pty Ltd for the approval of Hemangiol. For clarity this includes all correspondence, responses and appeal documentation.
- The TGA evaluation reports for this submission.
- The Therapeutic Goods legislation and EU guidelines published as adopted on the TGA website, especially
  - CPMP/ICH/2711/99: Clinical Investigation of Medicinal Products in the Paediatric Population, and
  - CPMP/EWP/2330/99: points to consider on Application with I. Meta-Analysis, 2. One Pivotal Study.
- The CHMP assessment report for Hemangiol
- The US FDA letter of approval for Hemangiol

Reasons

The legislation requires that in considering the registration of a good the Delegate shall assess whether the quality, safety and efficacy of the good for the purpose for which they are to be used have been satisfactorily established.

Quality has previously been accepted as satisfactory by the TGA.

The submission and information set out in the appeal establish that there is evidence of efficacy in the treatment of IH in patients requiring systemic therapy. The pivotal trial excluded those with life or function threatening complications but these were included and reported in all the supporting material. The consistency of treatment effect is seen in all material. As there is no evidence of a difference in pathophysiology of the IH lesions in these and those enrolled in the trial The Delegate of the Minister considered it is reasonable to extrapolate evidence of efficacy from the pivotal trial population to these patients.

Propranolol has a known safety profile that raises the possibility of serious AEs occurring in infants. In the trials presented and the CUP there were risk mitigation strategies put in place to minimise these events and use was restricted to those requiring systemic therapy, that is, not the majority of patients with uncomplicated IH. The safety profile in the pivotal trial demonstrated satisfactory safety for those patients requiring systemic therapy with these risk mitigation measures in place, including close monitoring of treatment under specialist care and with rules for exclusion and discontinuation of therapy.

Having considered the material submitted in the appeal, the original submission, initial decision, and the evaluation reports, the Delegate of the Minister concluded that there is satisfactory evidence of the quality, safety and efficacy of Hemangiol for the purpose for which it is to be used.

Conclusion

For the reasons referred to above, the Delegate of the Minister decided to revoke the initial decision and substitute the decision that Hemangiol oral solution containing propranolol hydrochloride 3.75 mg/mL should be included in the Australian Register of Therapeutic Goods for the indication:

Treatment of proliferating infantile hemangioma requiring systemic therapy:

- *Life-threatening hemangioma.*
- *Ulcerated hemangioma with pain and/or lack of response to simple wound care measures*
- *Hemangiomas with a risk of permanent scars or disfigurement.*

This decision is subject to application of the standard conditions applying to a prescription medicine entry, the submission of an acceptable revised product information document and the submission of an updated RMP based on the latest EU RMP (both ensuring risk mitigation strategies are in place including warnings to the effect that Hemangiol should only be used by specialists experienced in the management of IH), and a copy of an acceptable consumer medicine information document.

Final Outcome

The Delegate of the Secretary, in response to the sponsor's appeal under section 60 of the Therapeutic Goods Act1989 ('the 'Act'), under section 25AB of the Act made a decision under subsection 25(3) of the Act to approve the registration of Hemangiol propranolol 13.75 mg/mL oral solution. The approved indications for this therapeutic good are:

Treatment of proliferating infantile haemangioma requiring systemic therapy:

- *Life-threatening haemangioma.*
- *Ulcerated haemangioma with pain and/or lack of response to simple wound care measures.*
- *Hemangiomas with a risk of permanent scars or disfigurement.*

Specific conditions applying to this therapeutic good

1. The Hemangiol EU Risk Management Plan (EU-RMP), version 1.0 dated 27 February 2013 (data lock point 12 October 2012) with Australian Specific Annex included with submission PM-2013-01250-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The sponsor has described three studies of neurodevelopmental outcomes of children treated with Hemangiol in their correspondence with the TGA of 4 May and 10 June 2015, to be performed by [information redacted]. When available, the final study protocols and results of the individual studies should be submitted to the TGA, addressed to the Head of the Post Market Surveillance Branch.

Hemangiol (Propranolol hydrochloride; 3.75mg/mL oral solution) was entered on the ARTG on the 25 June 2015 (ARTG entry 212274).

Attachment 1. Product Information

The Product Information approved for Hemangiol at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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