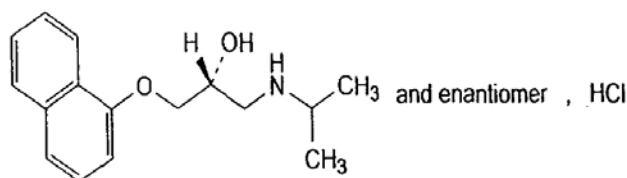


## PRODUCT INFORMATION

### **HEMANGIOL®** **3.75 mg/mL Oral Solution**

#### NAME OF THE MEDICINE

propranolol hydrochloride



CAS Registry Number: 318-98-9

#### DESCRIPTION

Propranolol hydrochloride is a white to off-white powder with the molecular formula  $C_{16}H_{21}NO_2 \cdot HCl$  and a molecular weight of 295.8. It is soluble in water and ethanol, slightly soluble in chloroform and practically insoluble in ether. It is non hygroscopic with a pKa of 9.5. Propranolol hydrochloride has a chiral centre; its synthesis produces a racemic mixture.

Hemangiol® drug product is presented as a colourless to slightly yellow, clear, oral solution with a fruity odour. One mL of Hemangiol® oral solution contains 3.75 mg of propranolol base (as propranolol hydrochloride 4.28 mg). Hemangiol® also contains the excipients: hydroxyethylcellulose, saccharin sodium, citric acid monohydrate, purified water and strawberry (proprietary ingredient number: 109091) and vanilla (proprietary ingredient number: 109044) flavours.

Attention is drawn to the difference in the labelling of the content of propranolol in Hemangiol® compared to other propranolol dosage forms: Hemangiol® solution is labelled in terms of the amount of *propranolol base* per mL whereas propranolol tablets are labelled in terms of the amount of *propranolol hydrochloride* per tablet.

Propylene glycol is the major component of the strawberry and vanilla flavours. Propylene glycol exposure is up to 2.08 mg/kg/day which does not present a

significant safety concern for the pediatric patient population, no risk for health of treated children is expected.

## PHARMACOLOGY

### Pharmacodynamics

Propranolol is a non-selective beta-blocker that is characterised by three pharmacological properties:

- The absence of cardioselective beta-1 beta-blocking activity;
- An antiarrhythmic effect;
- Lack of partial agonist activity (or intrinsic sympathomimetic activity).

The pathogenesis of infantile haemangioma remains poorly understood, however, neovascularisation and angiogenesis mechanisms are probably involved.

The effect of propranolol in proliferating infantile haemangioma could be attributed to the following proposed mechanisms described in the literature:

- Vasoconstriction: propranolol inhibits vasodilation via beta-receptors leading to vasoconstriction, thus inducing a reduction of blood flow within the haemangioma.
- Inhibition of angiogenesis: characterised by a decrease in the proliferation of vascular endothelial cells, a reduction of the neovascularisation and formation of vascular tubules, a reduction in the secretion of matrix metalloproteinase 9 (MMP-9) which is crucial for endothelial cell migration.
- Induction of apoptosis in capillary endothelial cells of haemangioma: beta-2 adrenoreceptors are expressed on the capillary endothelial cells. Their activation promotes the vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) signalling pathways and the resulting proangiogenesis/proliferation; their blockade by propranolol can inhibit capillary endothelial cell proliferation.

### Pharmacokinetics

#### Adults

##### Absorption

Studies with propranolol hydrochloride in humans indicate that it is almost completely absorbed from the intestine. A large part of the absorbed drug is lost to the systemic circulation due to the first pass metabolism in the liver. After repeated administration,

the first pass removal process becomes saturated and, at steady state, the plasma concentration is proportional to the dose, although there is some variation between patients as to the blood levels achieved at a given dose. In addition, correlation of plasma level to therapeutic effect varies considerably with propranolol as with some other  $\beta$ -blockers. Blood level measurements show that after intravenous administration, the concentration in the circulation decreases rapidly due mainly to uptake by tissues generally.

#### Bioavailability

In general, the peak blood level occurs between 1 and 3 hours after oral administration, and will have an average value of 0.1  $\mu\text{g/mL}$  per 80mg single dose. The peak blood level is proportional to the dose. With chronic administration the mean plasma half-life is from 3 to 6 hours, determined by clearance and plasma binding.

Following intravenous administration the plasma half-life of propranolol is about 2 hours and the ratio of metabolites to parent drug in the blood is lower than after oral administration. In particular 4-hydroxypropranolol is not present after intravenous administration.

#### Distribution

Propranolol is absorbed from the circulation and is widely distributed throughout the body tissues.

#### Protein binding

Approximately 93% is plasma bound in humans.

#### Metabolism

Propranolol is metabolised, primarily by the liver. Hydroxylation of the aromatic nucleus occurs with degradation of the isoprenaline side chain. Over 20 metabolites have been identified. One of these, the 4-hydroxy metabolite, found only after oral administration has  $\beta$ -adrenergic blocking properties.

#### Excretion

Some 95 to 100% of a dose of propranolol hydrochloride is excreted as metabolites and their conjugates in the urine.

#### Half-life

The plasma half-life of oral propranolol is of the order of 3 to 6 hours. The pharmacological effect lasts much longer.

### **Paediatric population**

The pharmacokinetics of propranolol and 4-OH-propranolol were evaluated in a multiple dose 12 week study conducted in 23 male and female infants 35 to 150 days

of age with haemangioma. The infants were stratified by age (35 to 90 days and 91 to 150 days). The starting dose was 1.2 mg/kg/day which was titrated to the target dose of 3.4 mg/kg/day in 1.1 mg/kg/day increments at weekly intervals. At steady state, following administration of 3.4 mg/kg/day twice daily, peak plasma propranolol concentrations were observed within 2 hours of oral administration. Clearance of propranolol in infants was similar across the age range studied (2.7 (SD=0.03) L/h/kg in infants <90 days of age and 3.3 (SD=0.35) L/h/kg in infants >90 days of age) and to that in adults when adjusted by body weight. The median elimination half-life of propranolol was about 3.5 hours. Plasma propranolol concentrations approximate a dose proportional increase in the dose range of 1.2 mg/kg/day to 3.4 mg/kg/day.

Plasma concentration of 4-OH-propranolol, the main metabolite, was about 5% of total plasma exposure of propranolol.

## **CLINICAL TRIALS**

For ethical reasons relating to the use of placebo, the demonstration of efficacy was not established in patients with high-risk infantile haemangioma (IH). Infants with life-threatening IH, function-threatening IH (e.g. those causing impairment of vision, or respiratory compromise caused by airway lesions), and/or complicated ulcerated IH were excluded from the clinical development program. Evidence of the efficacy of propranolol in patients with high-risk IH is based on studies reported in the literature and from a specific compassionate use program performed with propranolol.

The efficacy of propranolol for the treatment of proliferating infantile haemangioma requiring systemic therapy was established in a randomised, multidose, placebo-controlled, double-blind, multicentre, 2-stage adaptive phase II/III study in infants aged 5 weeks to 5 months at treatment initiation (Study 201).

At Stage 1, a total of 460 patients were randomised to 5 treatment arms (4 regimens of propranolol and placebo): 99 and 101 patients on propranolol 1 mg/kg/day and 3 mg/kg/day respectively for 3 months then placebo for 3 months; 103 and 102 patients on propranolol 1 mg/kg/day and 3 mg/kg/day respectively for 6 months; and 55 patients on placebo for 6 months. Propranolol dosing included a 3 week titration phase. Overall, 70% of patients had haemangiomas on the head and face and a majority of the haemangiomas were localised (89%).

At the end of Stage 1, an interim analysis for regimen selection was performed by an independent statistician on the first 190 randomised patients from all five regimens who had completed Week 24 (or prematurely withdrawn from treatment). The 'best' regimen (defined as the most efficacious regimen with a good safety profile) selected

for the primary efficacy analysis was propranolol 3 mg/kg/day for 6 months. Stage 2 comprised two treatment arms: placebo and the selected active regimen.

The primary efficacy analysis ITT data set comprised 55 patients in the placebo 6 months regimen and 101 patients in the 3 mg/kg/day 6 months regimen (Table 1). Treatment success was defined as a complete or nearly complete resolution of the target haemangioma at week 24 compared to baseline. Efficacy was assessed by evaluation of digital photographs by two blinded, independent, trained and validated readers.

Two patients (3.6%) in the placebo 6 month regimen and 61 patients (60.4%) in the 3 mg/kg/day 6 month regimen presented complete or nearly complete resolution of their haemangioma between baseline and Week 24 ( $p < 0.0001$ ). 11.4% of patients needed to be re-treated after treatment discontinuation.

**Table 1. Primary analysis results: Complete or nearly complete resolution at Week 24.**

<b>Primary endpoint - ITT</b>	<b>Placebo n=55</b>	<b>Propranolol 3 mg/kg/day 6 months n=101</b>	<b>P-value</b>
Yes	2 (3.6%)	61 (60.4%)	< 0.0001
No	53 (96.4%)	40 (39.6%)	
<b>Primary endpoint - PP</b>	<b>Placebo n=53</b>	<b>Propranolol 3 mg/kg/day 6 months n=93</b>	<b>P-value</b>
Yes	1 (1.9%)	56 (60.2%)	< 0.0001
No	52 (98.1%)	37 (39.8%)	

ITT: Intent-to-treat; PP: Per-protocol.

## INDICATIONS

Treatment of proliferating IH requiring systemic therapy:

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

## CONTRAINDICATIONS

The use in infants less than 5 weeks of age is contraindicated.

The use in infants less than 2.5kg is contraindicated.

- Hemangiol is contraindicated in premature infants for whom the corrected age of 5 weeks post-term has not been reached. The corrected age is calculated by subtracting the number of weeks of prematurity from the actual age (in weeks).
- Breastfed infants if the mother is treated with medicines contraindicated with propranolol.
- Hypersensitivity to propranolol or to any of the excipients.
- Asthma or a history of bronchospasm.
- Second- or third-degree atrioventricular blocks.
- Disease of the sinus node (including sinoatrial block).
- Bradycardia below the following limits:

Age	0-3 months	3-6 months	6-12 months
Heart rate (beats/min)	100	90	80

- Low blood pressure below the following limits:

Age	0-3 months	3-6 months	6-12 months
Blood pressure (mmHg)	65/45	70/50	80/55

- Cardiogenic shock.
- Heart failure not controlled by medication.
- Prinzmetal's angina.
- Severe peripheral arterial circulatory disturbances (Raynaud's phenomenon).
- Subjects prone to hypoglycaemia.
- Pheochromocytoma.

## **PRECAUTIONS**

### **Initiation of treatment**

Treatment with Hemangiol<sup>®</sup> should be initiated by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma, in a controlled clinical setting where adequate facilities for handling adverse events, including those requiring urgent measures, are available.

Prior to initiating propranolol therapy, screening for risks associated with propranolol use must be performed. An analysis of the medical history and a full clinical examination must be performed including heart rate, cardiac and pulmonary auscultation.

During the titration phase, each dose increase must be managed and monitored by a physician in the same conditions as the administration of the initial dose. After the titration phase, the dose will be readjusted by the physician according to the changes in the child's weight.

Clinical monitoring of the child's condition and dose readjustment need to be performed at least monthly.

In infants with a suspected cardiac abnormality, specialist advice must be sought before Hemangiol<sup>®</sup> initiation to determine any subjacent contra-indication.

In infants with an acute broncho-pulmonary abnormality, the initiation of Hemangiol<sup>®</sup> treatment should be postponed.

Parents or guardians should be advised to read the 'Consumer Medicine Information' and 'Handling Instructions' before use and instructed on the use of the oral dosing syringe. Parents or guardians should also be informed of the risk of hypoglycaemia, cardiovascular, respiratory and other risks associated with the use of Hemangiol<sup>®</sup> (see Hypoglycaemia, Heart Rate and Blood Pressure, Respiratory Disorders).

### **Hypoglycaemia**

Propranolol prevents the response of endogenous catecholamines to correct hypoglycaemia. It masks the adrenergic warning signs of hypoglycaemia, particularly tachycardia, shakiness, anxiety and hunger. It can aggravate hypoglycaemia in children, especially in the case of fasting, vomiting or overdose. These hypoglycaemic episodes associated with taking propranolol may present exceptionally in the form of seizures and/or coma.

If clinical signs of hypoglycaemia occur, it is necessary to make the child drink a sugary liquid solution and to temporarily stop the treatment. Appropriate monitoring of the child is required until symptoms disappear. In children with diabetes, blood glucose monitoring should be increased.

Parents or guardians should be informed that there is a risk of hypoglycaemia when Hemangiol® is given to infants who are not feeding regularly or who are vomiting. They should be instructed on how to recognise the signs of hypoglycaemia. Tell them to discontinue Hemangiol® and call their doctor immediately or take the child to the nearest hospital Accident and Emergency Department in case of suspected hypoglycaemia.

### **Bradycardia and Hypotension**

Propranolol, due to its pharmacological action, may cause or worsen bradycardia or blood pressure abnormalities. Bradycardia should be diagnosed if the heart rate declines by more than 30 bpm from baseline. Bradycardia is defined as a heart rate less than 80 bpm.

After the first intake and each dose increase, clinical monitoring, including blood pressure and heart rate must be performed at least hourly for at least 2 hours. In case of symptomatic bradycardia or bradycardia under 80 bpm, immediate specialist advice must be sought.

In case of severe and/or symptomatic bradycardia or hypotension occurring at any time during treatment, treatment must be discontinued and specialist advice should be sought.

Parents or guardians should be advised that there is a potential risk of bradycardia and hypotension associated with the use of Hemangiol®. They should be instructed to contact their doctor in case of fatigue, pallor, slow or uneven heart beats, peripheral coldness or fainting.

### **Respiratory disorders**

Propranolol can cause bronchospasm. In the event of lower respiratory tract infection associated with dyspnoea and wheezing, treatment with Hemangiol® should be temporarily discontinued. The administration of beta-2 agonists and inhaled corticosteroids might be required. The re-administration of Hemangiol® may be considered when the child has fully recovered. In infants with reoccurrence of respiratory symptoms, treatment with Hemangiol® should be permanently



discontinued. In infants with isolated bronchospasm following Hemangiol<sup>®</sup> exposure, Hemangiol<sup>®</sup> must be permanently discontinued.

Parents of guardians should be informed that Hemangiol<sup>®</sup> carries the risk of bronchospasm or exacerbation of lower respiratory tract infections. They should be instructed to contact their doctor or take their child to the nearest hospital Accident and Emergency Department if their child has breathing problems or wheezing during treatment with Hemangiol<sup>®</sup>.

### **Cardiac Failure**

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure. Its inhibition by beta blockade may precipitate more severe failure.

### **PHACE syndrome**

Very limited safety data of propranolol in PHACE syndrome patients are available. Propranolol may increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies by dropping blood pressure and attenuating flow through occluded, narrow or stenotic vessels.

Infants with large facial infantile haemangioma should be thoroughly investigated for potential arteriopathy associated with PHACE syndrome with magnetic resonance angiography of the head and neck and cardiac imaging to include the aortic arch, prior to considering propranolol therapy. Specialist advice should be sought.

### **Paediatric use**

Use in children aged less than 5 weeks post-term is contraindicated. Safety and effectiveness of Hemangiol<sup>®</sup> have not been established in this age group.

There are no clinical efficacy and safety data in the clinical studies carried out with Hemangiol<sup>®</sup> to recommend its initiation in children aged more than 5 months.

### **Use in lactation**

Propranolol passes through breast milk. Mothers being treated with propranolol who breastfeed their infant should inform their infant's treating physician before treatment is initiated in their child.

### **Liver or kidney impairment**

Hemangiol® is metabolised in the liver and excreted by the kidneys. In the absence of data in children, Hemangiol® is not recommended in infants with renal or hepatic impairment.

### **Hypersensitivity**

In patients likely to experience severe anaphylactic reaction, regardless of origin, particularly with iodinated contrast agents, beta-blocker treatment may lead to a worsening of the reaction and resistance to its treatment with adrenaline at normal doses.

### **General anaesthesia**

Beta-blockers will result in attenuation of reflex tachycardia and an increased risk of hypotension during surgery. In addition, beta-blockers can exacerbate bradycardias that can occur during general anaesthesia. When a patient is scheduled for surgery, beta-blocker therapy should be discontinued at least 48 hours prior to the procedure.

### **Hyperkalaemia**

Hyperkalaemia has been reported in patients with large ulcerated haemangioma. These patients should have their electrolytes monitored regularly.

### **Psoriasis**

A worsening of the disease has been reported with beta-blockers in patients suffering from psoriasis. Therefore, the need for treatment should be carefully weighed against this risk.

### **Effects on fertility**

Although some reversible effects on male and female fertilities were reported in adult rats receiving high doses of propranolol in the literature, the study performed in juvenile animals did not show any effect on fertility.

### **Genotoxicity**

Based on *in vivo* and *in vitro* data, propranolol is unlikely to pose a genotoxic risk to patients.

### **Carcinogenicity**

Long-term carcinogenicity studies conducted via dietary administration in mice and rats showed no evidence of tumourigenicity.

## **INTERACTIONS WITH OTHER MEDICINES**

In the absence of specific studies in children, potential drug interactions with Hemangiol® documented in this section are those which are known from studies in adults.

Interactions with Hemangiol® may occur:

- when the infant is being treated with any other medicines, notably those mentioned below and/or;
- when the infant is being breast fed by a mother taking any other medicines which may interact with Hemangiol®. In this case, the need to discontinue breast feeding should be discussed. Whenever stopping breastfeeding is considered, the benefits of breastfeeding should be weighed against the risks posed by the presence of the specific conditions listed.

Close clinical surveillance of any impaired tolerance of Hemangiol® is recommended.

### **Concomitant use not recommended**

*Bradycardia –inducing calcium-channel blockers (diltiazem, verapamil)*

Co-administration with propranolol can cause altered automaticity (excessive bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disorders, and increased risk of ventricular arrhythmias (torsades de pointes) along with heart failure.

This combination must only be administered under close clinical and ECG monitoring, particularly at the start of the treatment.

### **Interactions requiring caution**

#### **Cardiovascular drugs**

##### *Antiarrhythmics*

Propranolol exposure is increased by co-administration of propafenone. Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol despite a reassuring study in healthy volunteers.

The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two-three fold increased blood concentration and consequent increased beta-blockade that may cause postural hypotension.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta-blockers such as propranolol. Automatism

and conduction disorders are expected because of the suppression of sympathetic compensative mechanisms.

The metabolism of intravenous lidocaine is inhibited by co-administration of propranolol, resulting in a 25% increase in lidocaine concentrations. Lidocaine toxicity (neurological and cardiac adverse events) has been reported following co-administration with propranolol.

Caution should be exercised when administering propranolol with drugs that slow atrio-ventricular nodal conduction, e.g. digitalis, lidocaine and calcium channel blockers because of the risk of significant bradycardias.

#### *Digitalis glycosides*

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

#### *Dihydropyridines*

Caution should be exercised when patients receiving a beta blocker are administered a dihydropyridine. Both agents may induce hypotension, heart failure in patients whose cardiac function is partially controlled because of additive inotropic effects. Reduction of reflex sympathetic response involved when excessive distal vasodilatation.

#### *Calcium Channel Blockers*

Caution should be exercised when patients receiving a beta blocker are administered a calcium channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction. The mean  $C_{max}$  and AUC of propranolol are increased respectively by 50% and 30% by co-administration of nisoldipine and by 80% and 47% by co-administration of nifedipine. The mean  $C_{max}$  and AUC of nifedipine are increased by 64% and 79% respectively by co-administration of propranolol.

There have been reports of significant bradycardia, heart failure and cardiovascular collapse with concurrent use of verapamil and beta-blockers. Propranolol does not affect the pharmacokinetics of verapamil and norverapamil and conversely, verapamil does not affect the pharmacokinetics of propranolol. Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high-degree heart block and heart failure.

*Antihypertensives (ACE Inhibitors, angiotensin II-receptor antagonists, diuretics, alpha-blockers whatever the indication, centrally-acting antihypertensives, reserpine, etc)*

When combined with beta-blockers, drugs that decrease arterial pressure can cause or increase hypotension, notably orthostatic. With centrally-acting antihypertensives, beta-blockers may exacerbate the rebound hypertension after clonidine abrupt withdrawal, and propranolol should be stopped several days before discontinuing clonidine.

#### *ACE Inhibitors*

When combined with beta-blockers, ACE inhibitors can cause hypotension.

#### *Clonidine*

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Propranolol should be withdrawn several days before discontinuing clonidine (even in the case of clonidine treatment discontinuation for the breastfeeding mother).

#### *Alpha Blockers*

Prazosin has been associated with hypotension in the presence of beta-blockers.

#### *Reserpine*

Patients receiving catecholamine-depleting drugs such as reserpine, should be closely observed for excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks or orthostatic hypotension.

#### *Inotropic Agents*

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore relatively contraindicated in the treatment of propranolol overdose.

#### *Isoproterenol and Dobutamine*

Propranolol is a competitive inhibitor of beta-receptor agonists. Its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing investigation for myocardial ischemia.

#### *Sympathomimetic agents and Epinephrine*

Concomitant use of sympathomimetic agents e.g. epinephrine, may counteract the effect of beta-blocker drugs. Caution should be taken in the parenteral administration of preparations containing epinephrine in people taking beta-blockers as vasoconstriction, hypertension and reflex bradycardia may result.

### **Non-Cardiovascular drugs**

#### *Corticosteroids*

Patients with infantile haemangioma may be at increased risk if they have received or are concomitantly receiving treatment with corticosteroids because adrenal suppression may result in loss of the counter-regulatory cortisol response and increase the risk of hypoglycaemia. This also applies when children are breastfed by mothers treated with corticosteroids in case of high dosage or prolonged treatment.

#### *Nonsteroidal Anti-Inflammatory Drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to blunt the antihypertensive effect of beta-blockers.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

#### *Drugs inducing orthostatic hypotension (Nitrate derivatives, type 5-phosphodiesterase inhibitors, tricyclic antidepressants, antipsychotics, dopaminergic agonists, levodopa, amifostine, baclofen)*

Therapeutic classes which induce orthostatic hypotension may add their effects to that of beta-blockers.

Administration of zolmitriptan or rizatriptan with propranolol resulted in increased blood concentrations of zolmitriptan (AUC and  $C_{max}$  increased by 56% and 37% respectively) and rizatriptan (AUC and  $C_{max}$  increased by 67% and 75% respectively).

#### *Enzyme inducers*

Blood levels of propranolol may be decreased by co-administration of enzyme inducers like rifampicin or phenobarbital.

#### *Ergotamine*

Caution should be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol as arterial spasm with ischaemia of the extremities have been reported in a few patients. Clinical monitoring should be intensified, particularly during the first few weeks of co-administration.

#### *Theophylline*

Co-administration of theophylline with propranolol decreases oral theophylline clearance by 30% to 52%.

#### *Antidepressants*

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers.

#### *Benzodiazepines*

Propranolol can inhibit the metabolism of diazepam resulting in increased concentrations of diazepam and its metabolites. Diazepam does not alter the pharmacokinetics of propranolol. The pharmacokinetics of oxazepam, triazolam, lorazepam and alprazolam are not affected by co-administration of propranolol.

#### *Neuroleptic Drugs*

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol. Co-administration of long-acting propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 55% to 369% and increased thioridazine metabolite (mesoridazine) concentrations ranging from 33% to 209%. Co-administration of chlorpromazine with propranolol resulted in a 70% increase in propranolol plasma level.

#### *Baclofen*

Co-administration of baclofen with propranolol may increase the risk of hypotension, particularly postural hypotension. Blood pressure should be monitored and the antihypertensive dose adjusted, if necessary.

#### *Anti-Ulcer Drugs*

Co-administration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol AUC and  $C_{max}$  by 46% and 35%, respectively. Co-administration with aluminium hydroxide gel (1200 mg) may result in a decrease in propranolol concentrations. Co-administration of metoclopramide with long-acting propranolol did not have a significant effect on propranolol's pharmacokinetics.

#### *Hypoglycaemic agents*

Hemangiol<sup>®</sup> can mask certain symptoms and signs of hypoglycaemia such as palpitations and tachycardia. Use of Hemangiol<sup>®</sup> in patients with diabetes mellitus should be used with caution as it may exacerbate the response to insulin, resulting in hypoglycaemia. The parents/guardians of an infant with diabetes mellitus should be

informed of the risks of Hemangiol® treatment. The frequency of blood glucose monitoring should be increased, particularly at the start of treatment when the dose is being up-titrated

#### *Lipid Lowering Drugs*

Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations. Co-administration of propranolol with lovastatin or pravastatin decreased the AUC of lovastatin and pravastatin by 18 – 23% but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

#### *Halogenated Anaesthetic Agents*

Methoxyflurane and trichloroethylene may significantly depress myocardial contractility when administered with propranolol. Beta stimulating agents may be used to counteract the beta-blockade.

#### *Warfarin*

Concomitant administration of propranolol and warfarin has been shown to increase warfarin bioavailability and resultant prothrombin time.

#### *Alcohol*

Concomitant use of alcohol may increase plasma levels of propranolol.

## **ADVERSE EFFECTS**

In clinical trials for proliferating infantile haemangioma, the most frequently reported adverse drug reactions in infants treated with Hemangiol® were sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhoea and vomiting.

The most severe risks reported in the compassionate use program and in the literature concerned hypoglycaemia (and related events such as hypoglycaemic seizure) and aggravated respiratory tract infections with respiratory distress.

Adverse drug reactions observed in two clinical trials comprising 424 patients treated with Hemangiol® 1 mg/kg/day or 3 mg/kg/day for a maximum treatment duration of 6 months are presented in Table 2.



Frequency of adverse reactions is defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  and  $< 1/10$ ); uncommon ( $\geq 1/1000$  and  $< 1/100$ ); and not known (cannot be estimated from available data). Due to the clinical trial data base size, rare ( $\geq 1/10,000$  and  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) categories are not represented. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

**Table 2: Adverse reactions observed in infants with proliferating infantile haemangioma treated with Hemangiol®.**

System Organ Class	Very Common	Common	Uncommon	Not known
<b><i>Infections and infestations</i></b>	Bronchitis	Bronchiolitis		
<b><i>Metabolism and nutrition disorders</i></b>		Decreased appetite		
<b><i>Psychiatric disorders</i></b>	Sleep disorders	Agitation Nightmares Irritability		
<b><i>Nervous system disorders</i></b>		Somnolence		Hypoglycemic seizure
<b><i>Cardiac Disorders</i></b>			AV block	Bradycardia
<b><i>Vascular Disorders</i></b>		Peripheral coldness		Hypotension Vasoconstriction Raynaud's phenomenon
<b><i>Respiratory, thoracic and mediastinal disorders</i></b>		Bronchospasm		
<b><i>Gastro-intestinal Disorders</i></b>	Diarrhoea Vomiting	Constipation Abdominal pain		
<b><i>Skin and Subcutaneous Tissue Disorders</i></b>		Erythema	Urticaria Alopecia	
<b><i>Investigations</i></b>		Decreased blood pressure	Decreased blood glucose Decreased heart rate Neutropenia	Agranulocytosis Hyperkalemia

With lower respiratory tract infections like bronchitis or bronchiolitis, an aggravation of symptoms (including bronchospasm) has been observed in patients treated with Hemangiol® due to the bronchoconstrictive effect of propranolol. These effects rarely resulted in definitive treatment discontinuation (see PRECAUTIONS).

Sleep disorders were in the form of insomnia, poor quality of sleep and hypersomnia. Other CNS disorders were principally observed during the early periods of treatment.

Diarrhoea was frequently reported and was not always associated with an infectious gastrointestinal disease. The occurrence of diarrhoea seems to be dose-dependent between 1 and 3 mg/kg/day. None of the cases was severe nor led to treatment discontinuation.

Cardiovascular events reported during clinical studies were asymptomatic. During the 4 hours cardiovascular monitoring on the titration days, a decrease in heart rate (about 7 bpm) and of systolic blood pressure (less than 3 mmHg) was observed following drug administration. One case of second degree atrioventricular heart block in a patient with underlying conduction disorder led to definitive treatment discontinuation. Isolated cases of symptomatic bradycardia and hypotension have been reported in the literature.

Decreases in blood sugar observed during clinical studies were usually asymptomatic. However, several reports of hypoglycaemia with related seizure were reported during the compassionate use program, especially in cases of altered glucose intake during intercurrent illness (see PRECAUTIONS).

Concomitant treatment with systemic corticosteroids may increase the risk of hypoglycaemia (see INTERACTIONS WITH OTHER MEDICINES).

Hyperkalemia has been reported in the literature in a few patients with large ulcerated haemangioma.

## **DOSAGE AND ADMINISTRATION**

### **Dosage**

Hemangiol® should be initiated in infants aged 5 weeks post-term to 5 months.

The dosage is expressed in propranolol base.

The recommended starting dose of Hemangiol® is 0.15 mL/kg (0.5 mg/kg) (see Table 3) 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.

**Table 3: Dose titration according to weight.**

	<b>Week 1</b>	<b>Week 2</b>	<b>Week 3 (maintenance)</b>
<b>Weight (kg)</b>	<b>Volume administered twice a day</b>	<b>Volume administered twice a day</b>	<b>Volume administered twice a day</b>
2.5 to <3.0	0.4 mL	0.8 mL	1 mL
3.0 to <3.5	0.5 mL	0.9 mL	1.2 mL
3.5 to <4.0	0.5 mL	1.1 mL	1.4 mL
4 to <4.5	0.6 mL	1.2 mL	1.6 mL
4.5 to <5.0	0.7 mL	1.4 mL	1.8 mL
5 to <5.5	0.8 mL	1.5 mL	2.0 mL
5.5 to <6.0	0.8 mL	1.7 mL	2.2 mL
6 to <6.5	0.9 mL	1.8 mL	2.4 mL
6.5 to <7.0	1.0 mL	2.0 mL	2.6 mL
7 to <7.5	1.1 mL	2.1 mL	2.8 mL
7.5 to <8.0	1.1 mL	2.3 mL	3.0 mL
8 to <8.5	1.2 mL	2.4 mL	3.2 mL
8.5 to <9.0	1.3 mL	2.6 mL	3.4 mL
9 to <9.5	1.4 mL	2.7 mL	3.6 mL
9.5 to <10	1.4 mL	2.9 mL	3.8 mL
10 to <10.5	1.5 mL	3.0 mL	4.0 mL

10.5 to <11	1.6 mL	3.2 mL	4.2 mL
11 to <11.5	1.7 mL	3.3 mL	4.4 mL
11.5 to <12	1.7 mL	3.5 mL	4.6 mL
12 to <12.5	1.8 mL	3.6 mL	4.8 mL

## **Administration**

To reduce the risk of hypoglycaemia, administer Hemangiol® orally during or immediately after a feeding. Skip the dose if the child is not eating or is vomiting (see PRECAUTIONS, Hypoglycaemia).

Monitor heart rate and blood pressure for 2 hours after Hemangiol® initiation or dose increases (see PRECAUTIONS, Bradycardia and Hypotention).

The dose should be delivered directly into the child's mouth using the graduated oral syringe, calibrated in mL of propranolol base, which is supplied with the product. The bottle should not be shaken before use.

If necessary, Hemangiol® oral solution may be diluted in a small quantity of breast milk or age-adapted apple or orange juice and delivered to your child in a baby's bottle. Hemangiol® should not be mixed with a full bottle of milk or juice. For children weighing up to 5 kg, the Hemangiol® dose may be mixed with one teaspoonful of milk (approximately 5 mL). For children weighing more than 5 kg, the dose may be mixed with a tablespoonful of milk or fruit juice (approximately 15mL).

Use the mixture within 2 hours of preparation

Ideally, Hemangiol® should be given to the child by the same person in order to avoid the risk of accidental overdose and hypoglycaemia. If different carers are involved, good communication is essential in order to ensure the safety of the child.

If the child is not eating or is vomiting, it is recommended that the child miss the next dose. In case the child regurgitates the dose or does not take all of the medicine, no other dose should be given before the next scheduled dose.

Clinical monitoring of the child's condition and dose readjustment should be performed at least monthly.

## **Duration of treatment**

Hemangiol® should be administered for a 6-month period. Discontinuation of treatment does not require tapering of the dose.

If haemangiomas recur, treatment may be re-initiated. Based on data from the literature, 10 to 25% of patients showed a relapse of haemangioma signs and symptoms after treatment discontinuation. When treatment was re-initiated, a satisfactory response was observed in a majority of patients.

## **OVERDOSAGE**

The toxicity of beta-blockers is an extension of their therapeutic effect. Cardiac symptoms of mild to moderate poisoning are decreased heart rate and hypotension. Atrioventricular blocks, intraventricular conduction delays and congestive heart failure can occur with more severe poisoning. Bronchospasm may develop particularly in patients with asthma. Hypoglycaemia may develop and manifestations of hypoglycaemia (tremor, tachycardia) may be masked by other clinical effects of beta-blocker toxicity.

Propranolol is highly lipid-soluble and may cross the blood brain barrier and cause seizures.

## **Support and treatment**

In the event of overdose, monitor the patient's airway, breathing & circulation; cardiac monitoring should be performed; assess vital signs, mental status and blood glucose. Give intravenous fluids for hypotension and atropine for bradycardia. Glucagon then catecholamines should be considered if the patient does not respond appropriately to intravenous fluid. Isoproterenol and aminophylline may be used to treat bronchospasm.

## **PRESENTATION**

Hemangiol® is available as a 3.75 mg/mL oral solution in a 120 mL amber-glass type III bottle fitted with a low density polyethylene insert and closed with a child-resistant, tamper-evident polypropylene screw cap. It is supplied with a 5 mL polypropylene oral syringe. The syringe is graduated in mL of propranolol base.

## **STORAGE CONDITIONS**

Store below 30°C. Do not freeze.  
Use within 2 months of opening.  
Protect from light.

## **NAME AND ADDRESS OF THE SPONSOR**

Pierre Fabre Australia Pty Limited  
Suite 601, 504 Pacific Highway  
St Leonards NSW 2065  
Australia

## **POISON SCHEDULE**

S4

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

25 June 2015