SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hemangiol, 3.75 mg/mL oral solution

Caregiver guide
The marketing of Hemangiol is subject to a risk management plan (RMP) including a 'caregiver guide' for the patient's parents. The 'caregiver guide', emphasizes important safety information that the patient's parents should be aware of before and during treatment. Please explain to the patient's parents the need to read the 'caregiver guide' before starting treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 4.28 mg of propranolol hydrochloride equivalent to 3.75 mg of propranolol base.

Excipients with known effect:
1 ml of solution contains 2.60 mg Propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear, colourless to slightly yellow oral solution, with a fruity odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hemangiol is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy:
- Life- or function-threatening haemangioma,
- Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,
- Haemangioma with a risk of permanent scars or disfigurement.

It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2).

4.2 Posology and method of administration

Treatment with Hemangiol 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 of adverse reactions, including those requiring urgent measures, are available.

Posology
The posology is expressed in propranolol base.
The recommended starting dose is 1 mg/kg/day which is divided into two separate doses of 0.5 mg/kg. It is recommended to increase the dose up to the therapeutic dose under medical supervision as follows: 1 mg/kg/day for 1 week, then 2 mg/kg/day for 1 week and then 3 mg/kg/day as a maintenance dose.
The therapeutic dose is 3 mg/kg/day, which is to be administered into 2 separate doses of 1.5 mg/kg, one in the morning and one in late afternoon, with a time interval of at least 9 hours between two intakes. Hemangiol is to be given during or right after a feed to avoid the risk of hypoglycaemia.
If the child is not eating enough or is vomiting it is recommended to skip the dose.
In case the child spits up a dose or does not take all of the medicinal product, no other dose should be given before the next scheduled dose.

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 condition, and dose readjustment, need to be performed at least monthly.

Duration of treatment:
Hemangiol should be administered for a 6-month period.
Discontinuation of treatment does not require a progressive decrease in the dose.
In the minority of patients showing a relapse of symptoms after treatment discontinuation, treatment may be re-initiated under the same conditions with a satisfactory response.

Paediatric populations
In the absence of clinical efficacy and safety data, Hemangiol should not be used in infants aged below 5 weeks.
There is no clinical efficacy and safety data in the clinical studies carried out with Hemangiol to recommend its initiation in infants and children aged above 5 months.

Infants with hepatic or renal impairment
In the absence of data, administration of the medicinal product is not recommended to infants with hepatic or renal impairment (see section 4.4).

Method of administration
Oral use.
Hemangiol should be administered directly into the child's mouth using the graduated oral syringe, calibrated in mg of propranolol base, supplied with the oral solution bottle (see instructions for use in section 3 of the patient information leaflet).
The bottle should not be shaken before use.
If necessary, the medicinal product may be diluted in a small quantity of baby-milk or age-adapted apple and/or orange fruit juice. The medicine should not be put in the full filled bottle. The mixing may be done with one teaspoonful (approximately 5 mL) of milk for children weighing up to 5 kg, or with a tablespoonful (approximately 15 mL) of milk or fruit juice for

children weighing more than 5 kg, delivered in a baby's bottle. The mixing should be used within 2 hours.
Hemangiol and the feed must be given by the same person in order to avoid the risk of hypoglycaemia. If different people are involved, good communication is essential in order to ensure the safety of the child.

4.3 Contraindications

- Premature infants, for whom the corrected age of 5 weeks has not been reached (the corrected age being calculated by subtracting the number of weeks of prematurity from the actual age)
- Breastfed infants, if the mother is treated with medicinal products contraindicated with propranolol
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Asthma or 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 treatment
- Prinzmetal's angina
- Severe peripheral arterial circulatory disturbances (Raynaud's phenomenon)
- Infants prone to hypoglycaemia
- Phaeochromocytoma

4.4 Special warnings and precautions for use

Initiation of treatment
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.
In case of suspected cardiac abnormality, a specialist advice must be sought before treatment initiation to determine any subjacent contra-indication.
In case of acute broncho-pulmonary abnormality, the initiation of the treatment should be postponed.

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 during fasting period

(e.g. poor oral food intake, infection, vomiting), when glucose demands are increased (cold, stress, infections), or in case of overdose.
Hypoglycaemic episodes associated with the taking of 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.

Prescribers should inform carers/parents on the risk of serious hypoglycaemia that remains equally prominent throughout the whole treatment period and emphasize the need to respect the dosing recommendations **(**see section 4.2).

Carers should be provided guidance on how to recognise the clinical signs of hypoglycaemia in order to:

- immediately treat the hypoglycaemic condition to prevent life-threatening situations,
- contact a doctor or to go straight to hospital,
- discontinue the treatment.

In children with diabetes, blood glucose monitoring should be more frequent and followed by the endocrinologist.

Respiratory disorders
In the event of lower respiratory tract infection associated with dyspnoea and wheezing, treatment should be temporarily discontinued. The administration of beta2 agonists and inhaled corticosteroids is possible. The readministration of propranolol may be considered when the child has fully recovered; in case of reoccurrence, treatment should be permanently discontinued.
In the event of isolated bronchospasm, treatment must be permanently discontinued.

Cardiovascular disorders
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 below the following limits:

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

After the first intake and each dose increase, a 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 a specialist advice should be sought.

Cardiac Failure:
Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. In children with cardiac failure, the treatment should be managed by the cardiologist.

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 hemangioma 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.
Specialized advice should be sought.

Breast-feeding:
Propranolol passes through breast milk, mothers being treated with propranolol who breastfeed their infant should inform their health care professional.

Liver or kidney failure
Propranolol is metabolised in the liver and excreted by the kidneys. In the absence of data in children, propranolol is not recommended in case of renal or hepatic impairment (see section 4.2).

Hypersensitivity
In patients likely to experience severe anaphylactic reaction, regardless of origin, particularly with iodinated contrast agents, beta-blocker treatment may lead to worsening of the reaction and resistance to its treatment with adrenaline at normal doses. In children who are at risk of anaphylaxis, the benefit risk of the medicinal product should be evaluated.

General anaesthesia
Beta-blockers will result in an attenuation of reflex tachycardia and an increased risk of hypotension. It is necessary to alert the anaesthetist to the fact that the patient is being treated with beta-blockers.
When a patient is scheduled for surgery, beta-blocker therapy should be discontinued at least 48 hours prior to the procedure.

Hyperkaliemia
Hyperkaliemia cases have been reported in patients with large ulcerated hemangioma. A monitoring of electrolyte should be performed in these patients.

Psoriasis
Worsening of disease has been reported with beta-blockers in patients suffering from psoriasis. Therefore the need for treatment should be carefully weighed up.

Excipients with known effects
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free’.
This medicinal product contains 2.08 mg of propylene glycol/kg/day. Caution should be taken into account in babies less than 4 weeks old, in particular if the baby is given other medicines that contain propylene glycol or alcohol.
Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicinal products and other forms of interaction

In the absence of specific studies in children, the drug interactions with propranolol are those

known in adults. Combinations should consider the 2 following situations (not mutually exclusive):

- infants given any other medicinal products, notably those mentioned below.
- infants breastfed by mothers taking any other medicinal products, notably those mentioned below. In this case, the need of stopping breast-feeding should be discussed.

A close clinical surveillance of any impaired tolerance of propranolol is requested.

Concommitant use not recommended

Bradycardia –inducing calcium-channel blockers (diltiazem, verapamil, bepridil)
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 precautions for use

Cardiovascular Medicinal Products

Antiarrhythmics

- Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.
- The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two-three-fold increased blood concentration and greater degrees of clinical beta-blockade.
- Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-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.

Digitalis glycosides
Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. The advice of a cardiologist should be sought.

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

Antihypertensives (*ACE Inhibitors, angiotensin II-receptors antagonists, diuretics, alpha-blockers whatever the indication, centrally-acting antihypertensives, reserpine, etc)*
When combined with beta-blockers, medicinal products that decrease arterial pressure can cause or increase hypotension, notably orthostatic. With regard to *centrally-acting antihypertensives,* beta-blockers may exacerbate the rebound hypertension after clonidine abrupt withdrawal, and propranolol should be stopped several days before discontinuing

clonidine.

Non-Cardiovascular Medicinal Products

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 counterregulatory 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 (see section 4.4 concerning hypoglycaemia).

Medicinal products inducing orthostatic hypotension
Medicinal products that induce postural hypotension (nitrates derivatives, type 5-phosphodiesterase inhibitors, tricyclic antidepressants, antipsychotics, dopaminergic agonists, levodopa, amifostine, baclofen…) may add their effects to that of beta-blockers. The advice of a cardiologist should be sought.

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

Hypoglycaemic agents
All beta-blocking agents can mask certain symptoms of hypoglycaemia: palpitations and tachycardia.
Use of propranolol alongside hypoglycaemic therapy in diabetic patients should be with caution since it may prolong the hypoglycaemic response to insulin. In this case, inform the caregiver, and increase monitoring of blood glucose levels, particularly at the start of treatment.

Lipid lowering medicinal products
Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Halogenated Anesthetic Agents
They may depress myocardial contractility and vascular compensating response when administered with propranolol. Beta stimulating agents may be used to counteract the beta-blockade.

4.6 Fertility, pregnancy and lactation

Pregnancy
Not relevant.

Breast-feeding
Breastfeeding mothers: see section 4.4 and section 4.5.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials for proliferating infantile haemangioma, the most frequently reported adverse reactions in infant treated with Hemangiol were sleep disorders (16.7%), aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhea (16.5%), and vomiting (11.5%).

Globally, the adverse reactions reported in the compassionate use program and in literature concerned hypoglycemia (and related event like hypoglycaemic seizure) and aggravated respiratory tract infections with respiratory distress.

Tabulated list of adverse reactions

The following table gives the adverse reactions, reported whatever dose and treatment duration, in three clinical studies, including 435 patients treated by Hemangiol at 1 mg/kg/day or 3 mg/kg/day for a maximum treatment duration of 6 months.

Their frequency is defined using the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Due to the clinical trial database size rare and very rare categories are not represented.

Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

	Very Common	**Common**	**Uncommon**	**Not known**
Infections and infestations	Bronchitis	Bronchiolitis		
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders	Sleep disorder	Agitation Nightmares Irritability		
Nervous system disorders		Somnolence		Hypoglycemic seizure
Cardiac disorders			AV block	Bradycardia
Vascular disorders		Peripheral coldness		Hypotension Vasoconstriction Raynaud's phenomenon

	Very Common	Common	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders		Bronchospasm		
Gastrointestinal disorders	Diarrhea Vomiting	Constipation Abdominal pain		
Skin and subcutaneous tissue disorders		Erythema Dermatitis diaper	Urticaria Alopecia	Dermatitis psoriasiform
Investigations		Decreased blood pressure	Decreased blood glucose Decreased heart rate Neutropenia	Agranulocytosis Hyperkaliemia

Description of selected adverse reactions

Concerning the 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 led to definitive treatment discontinuation (see section 4.4).

Sleep disorders corresponded to insomnia, poor quality of sleep and hypersomnia. Other Central Nervous System disorders were principally observed during the early periods of treatment.

Diarrhea was frequently reported and was not always associated with an infectious gastrointestinal disease. The occurrence of diarrhea seems to be dose-dependent between 1 and 3 mg/kg/day. None of cases was of severe intensity and led to treatment discontinuation.

Cardiovascular events reported during clinical studies were asymptomatic. In the context of the 4 hours cardiovascular monitoring during the titration days, it was observed a decrease of heart rate (about 7 bpm) and of systolic blood pressure (less than 3 mmHg) 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 literature.

Blood sugar decreases observed during clinical studies were asymptomatic. However, several reports of hypoglycaemia with related hypoglycaemic seizure were reported during the compassionate use program and in literature, especially in case of fasting period during intercurrent illness (see section 4.4).

Concomitant treatment with systemic corticosteroids may increase the risk of hypoglycemia (see section 4.5).

Hyperkalaemia has been reported in the literature in few patients with large ulcerated haemangioma (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.health.gov.il

Additionally, you can also report to Padagis via the following address: Padagis.co.il.

4.9 Overdose

The toxicity of beta-blockers is an extension of their therapeutic effects:

- 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.
- Hypoglycemia may develop and manifestations of hypoglycemia (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:
The patient should be placed on a cardiac monitor, monitor vital signs, mental status and blood glucose. Intravenous fluids for hypotension and atropine for bradycardia should be given. Glucagon then catecholamines should be considered if the patient does not respond appropriately to intravenous fluid. Isoproterenol and aminophylline may be used for bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-Blocking agent, non-selective, ATC code: C07AA05

Mechanism of action
Potential mechanisms of action of propranolol in proliferating infantile haemangioma described in the literature could include various mechanisms all in close relationship:

- a local haemodynamic effect (vasoconstriction which is a classical consequence of beta-adrenergic blockade and a decrease of infantile haemangioma lesion perfusion);
- an antiangiogenic effect (decrease of vascular endothelial cells proliferation, reduction of the neovascularization and formation of vascular tubules, reduction of the secretion of Matrix Metalloproteinase 9);
- an apoptosis-triggering effect on capillary endothelial cells;
- a reduction of both VEGF and bFGF signalling pathways and subsequent angiogenesis / proliferation.

Pharmacodynamic effects
Propranolol is a 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).

Clinical efficacy and safety in the paediatric population
The efficacy of propranolol in infants (aged 5 weeks to 5 months at treatment initiation) with proliferating infantile haemangioma requiring systemic therapy has been demonstrated in a pivotal randomised, controlled, multicentre, multidose, adaptive phase II/III study aimed to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind).

Treatment was administered to 456 subjects (401 Propranolol at a dose of 1 or 3 mg/kg/day for 3 or 6 months; 55 Placebo), including a titration phase over 3 weeks. Patients (71.3% female; 37% aged 35-90 days old and 63% aged 91-150 days old) presented a target haemangioma on the head in 70% and majority of the infantile haemangiomas were localized (89%).

Treatment success was defined as a complete or nearly complete resolution of the target haemangioma, which was evaluated by blinded centralized independent assessments made on photographs at Week 24, in the absence of premature treatment discontinuation.

The regimen 3 mg/kg/day during 6 months (selected at the end of the phase II part of the study) presented 60.4% of success versus 3.6% in the placebo arm (p value < 0.0001). Age (35-90 days / 91-150 days), gender and haemangioma location (head / body) subgroups did not identify differences in response to propranolol. Improvement of haemangioma was observed at 5 weeks of treatment by propranolol in 88% of patients. 11.4% of patients needed to be re-treated after treatment discontinuation.
For ethical reasons related to the use of placebo, the demonstration of the efficacy was not established in patients with high-risk haemangioma. Evidence of the efficacy of propranolol in patients with high-risk haemangioma is available both in literature and in a specific compassionate use program performed with Hemangiol.

Based on a retrospective study, a minority of patients (12%) required a re-initiation of systemic treatment. When treatment was re-initiated, a satisfactory response was observed in a large majority of patients.

5.2 Pharmacokinetic properties

Adults
Absorption and distribution:
Propranolol is almost completely absorbed after oral administration. However, it undergoes an extensive first-pass metabolism by the liver and on average only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1 to 4 hours after an oral dose. Administration of protein-rich foods increases the bioavailability of propranolol by about 50% with no change in time to peak concentration.

Propranolol is a substrate for the intestinal efflux transporter, P-glycoprotein (P-gp). However, studies suggest that P-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and alpha1

acid glycoprotein). The volume of distribution of propranolol is approximately 4 L/kg. Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

Biotransformation and elimination:
Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. The percentage contributions of these routes to total metabolism are 42%, 41% and 17%, respectively, but with considerable variability between individuals. The four major final metabolites are propranolol glucuronide, naphthyloxylactic acid and glucuronic acid, and sulfate conjugates of 4-hydroxy propranolol. *In vitro* studies indicated that CYP2D6 (aromatic hydroxylation), CYP1A2 (chain oxidation) and to a less extent CYP2C19 were involved in propranolol metabolism.

In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers and poor metabolizers with respect to oral clearance or elimination half-life.
The plasma half-life of propranolol ranges from 3 to 6 hours. Less than 1% of a dose is excreted as unchanged drug in the urine.

Paediatric population
The pharmacokinetics of repeated administrations of Hemangiol at 3 mg/kg/day given in 2 intakes has been investigated in 19 infants aged 35 to 150 days at the beginning of treatment. The pharmacokinetic evaluation was performed at steady-state, after 1 or 3 months of treatment.

Propranolol was rapidly absorbed, the maximum plasma concentration generally occurring 2 hours after administration with a corresponding mean value around 79 ng/mL whatever the infant age.
Mean apparent oral clearance was 2.71 L/h/kg in infants aged 65- 120 days and 3.27 L/h/kg in infant aged 181- 240 days. Once corrected by the body weight, primary pharmacokinetic parameters for propranolol (such as plasma clearance) determined in infants were similar to those reported in the literature for adults.
The 4-hydroxy-propranolol metabolite was quantified, its plasma exposure accounting for less than 7% of the parent drug exposure.

During this pharmacokinetic study including infants with function-threatening haemangioma, haemangioma in certain anatomic locations that often leave permanent scars or deformity, large facial haemangioma, smaller haemangioma in exposed areas, severe ulcerated haemangioma, pedunculated haemangioma, efficacy was also studied as a secondary evaluation criteria. Treatment with propranolol resulted in a rapid improvement (within 7-14 days) in all patients and resolution of the target haemangioma was observed in 36.4% of patients by 3 months.

5.3 Preclinical safety data

In animals, after an acute dosing, propranolol is considered as a moderately toxic drug with an oral LD50 of about 600 mg/kg. The main effects reported after repeated administration of propranolol in adult and juvenile rats were a transient decrease in body weight and body weight gain associated with a transient decrease in organ weight. These effects were completely reversible when treatment was discontinued.

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.
Although some data were equivocal, based on the overall available *in vitro* and *in vivo* data, it can be concluded that propranolol is devoid of genotoxic potential.

In adult female rats, propranolol given into the uterus or by intravaginal administration is a powerful anti-implantation agent at dose ≥4 mg per animal, the effects being reversible. In adult male rats, repeated administration of propranolol at high dose levels (≥7.5 mg/kg) induced histopathological lesions of the testes, epididymis, and seminal vesicles, decrease in sperm motility, sperm cell concentration, plasma testosterone levels and significant increase in sperm head and tail abnormalities. The effects generally totally reversed after treatment cessation. Similar results were obtained following intra-testicular administration of propranolol and using in vitro models. However, in the study conducted in juvenile animals treated all over the development period corresponding to infancy, childhood and adolescence, no effect on male and female fertilities was observed (See section 4.6).

The potential effects of propranolol on the development of juvenile rats were evaluated following daily oral administration from post-natal Day 4 (PND 4) to PND 21 at dose-levels of 0, 10, 20 or 40 mg/kg/day.
Mortality with unknown although unlikely relationship to treatment was observed at 40 mg/kg/day, leading to a NOAEL of 20 mg/kg/day for juvenile toxicity.
In terms of reproductive development, growth and neurological development there were no propranolol-related effects or toxicologically significant findings at 40 mg/kg/day, correlating to safety margins of 1.2 in females and 2.9 in males, based on mean propranolol exposures on PND 21.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydroxyethylcellulose (250 grade)
- Vanilla flavour (IFF*SC011851)(contains propylene glycol 75.2%, Vanillin, Water, Butyric acid, Ethyl butyrate, Piperonal)
- Saccharin sodium
- Strawberry flavour (IFF*SN864761)[contains propylene glycol 92%, Ethyl butyrate, Vanillin, Undecalactone/Gamma, Ethyl acetate, Ethyl propionate, Maltol, Hydroxy-2-5-dimethyl-3(2h)-furanone/4-, Hexyl alcohol, Hexen-1-Ol/Cis-3, Linalool, Isoamyl butyrate, Ethylhexanoate, Ethyl-2-methylbutyrate, Hexen-1-YI acetate/Cis-3-, Decalactone/gamma-, Methylbutyric acid/2-, Hydroxyphenyl)-2-butanone/4(para-, Methyl dihydrojasmonate, Methyl cinnamate, Ethyl Isovalerate, Hexenal/trans-2-, Hexanoic acid, diacetyl natural, Isovaleric acid, Ionone/alpha, Ionone/beta, Ionone/gamma, Tocopherol/alpha]
- Citric acid monohydrate
- Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening: 2 months.

6.4 Special precautions for storage

Store below 25°C.Keep the bottle in the original carton in order to protect from light.
Do not freeze.
Store the bottle and the oral syringe in the outer carton between each use.

6.5 Nature and contents of container

120 mL solution, in a type III amber-glass bottle fitted with polyethylene insert and a child resistant polypropylene screw cap, provided with a polypropylene oral syringe graduated in mg of propranolol base.
Pack size: carton containing 1 bottle and 1 oral syringe.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Padagis Israel Agencies Ltd.,1 Rakefet St., Shoham

8. MANUFACTURER

PIERRE FABRE
MEDICAMENT
LES
CAUQUILLOUS,
81500 LAVAUR,
FRANCE

9. REGISTRATION NUMBER

159-68-35287-00

Revised in July 2023 according to MOHs guidelines.

17.07.2023