

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

HEMANGIOL 3.75 mg/mL oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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. The medicinal product is to be taken during or right after a feed.

If the child is not eating 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 medicine, 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.

Specific populations

In the absence of clinical efficacy and safety data, HEMANGIOL should not be used in children 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 children aged above 5 months.

Infants with hepatic or renal impairment

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

Method of administration

For oral use.

HEMANGIOL is to be given during or right after a feed to avoid the risk of hypoglycaemia. It 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. Don't put the medicine in the full 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 medicines 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 medication

- Prinzmetal's angina
- Severe peripheral arterial circulatory disturbances (Raynaud's phenomenon)
- Infants prone to hypoglycaemia
- Pheochromocytoma

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.

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.

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 case of fasting, vomiting or overdose.

These 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.

In children with diabetes, blood glucose monitoring should be increased.

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.

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.

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.

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.

Hyperkalemia

Hyperkalemia 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.

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.

Concomitant 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 caution

Cardiovascular Medicinal Products

Antiarrhythmics

- 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 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.

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, drugs 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.

Nonsteroidal Anti-Inflammatory Drugs

Non steroidal anti-inflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-blocking agents.

Drugs inducing orthostatic hypotension

Drugs 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.

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, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhoea, and vomiting.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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		

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

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. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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 Hemangirol.

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
- Sodium saccharin
- Strawberry flavour (contains propylene glycol)
- Vanilla flavour (contains propylene glycol)
- 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

Before opening: 3 years.

After first opening: 2 months.

6.4 Special precautions for storage

Keep the bottle in the original carton in order to protect from light.

Do not freeze.

Store the bottle and the syringe together in the carton box between each use.

6.5 Nature and contents of container

120 mL solution, in an amber-glass bottle fitted with a low density polyethylene insert and a child resistant polypropylene screw cap, provided with a polypropylene oral syringe graduated in mg of propranolol base.

Pack size: 1.

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

PIERRE FABRE DERMATOLOGIE

45 place Abel Gance

F- 92100 Boulogne

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/14/919/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Farnea
10, rue Bouché Thomas
ZAC d'Orgemont
F-49000 Angers
France

PIERRE FABRE MEDICAMENT PRODUCTION - CHATEAURENARD
Site SIMAPHAC, Zone Industrielle de Chateaurenard
45220 CHATEAURENARD
France

PIERRE FABRE MEDICAMENT PRODUCTION
Site PROGIPHARM, Rue du Lycée
45500 GIEN
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack for the proposed indication, targeting all caregivers who are expected to prepare and administer HEMANGIOL to children. This educational pack is aimed at increasing awareness about the potential risk of hypotension, bradycardia, and bronchospasm, after taking HEMANGIOL, and providing guidance on how to monitor/manage that risk.

It is also aimed to instruct caregivers to correctly feed the children during treatment in order to avoid the risk of hypoglycaemia.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution prior to the launch of the new indication (treatment of proliferating infantile haemangioma) in the Member State.

The educational materials for caregivers treating children with HEMANGIOL should include the following key safety elements:

- Information on the conditions for which HEMANGIOL should not be given
- Information on the correct procedure of product preparation and administration including:
 - Instructions on how to prepare the solution with HEMANGIOL
 - Advice on how to feed children during treatment
 - Information on how to detect and manage any sign of hypoglycaemia during treatment with HEMANGIOL
 - Instructions on when to discontinue the administration of HEMANGIOL
- The need to monitor and to contact the healthcare professionals if the following signs and symptoms occur after treatment:
 - For bradycardia and hypotension: fatigue, coldness, pallor, bluish-coloured skin, and fainting.
 - For hypoglycaemia: minor symptoms like pallor, tiredness, sweating, shakiness, palpitations, anxiety, hunger, difficulty waking up; major symptoms like excessive sleeping, difficulty to get a response, poor feeding, temperature decrease, convulsions (fits), brief pauses in breathing, loss of consciousness

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON BOX / BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

HEMANGIOL 3.75 mg/mL, oral solution
Propranolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution.
120 mL.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Use with oral syringe graduated in mg of propranolol included in the package. Do not use any other measuring device.
Do not shake the bottle before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, the medicine should be used within 2 months.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.
Store the bottle and syringe together in the outer carton between each use. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

PIERRE FABRE DERMATOLOGIE
45 place Abel Gance
F- 92100 Boulogne

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/919/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

HEMANGIOL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

B. PACKAGE LEAFLET

Package leaflet: Information for the user

HEMANGIOL 3.75 mg/mL, oral solution Propranolol

Read all of this leaflet carefully before your child starts receiving this medicine because it contains important information.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What HEMANGIOL is and what it is used for
2. What you need to know before your child receives HEMANGIOL
3. How HEMANGIOL is given
4. Possible side effects
5. How to store HEMANGIOL
6. Contents of the pack and other information

1 What HEMANGIOL is and what it is used for

What HEMANGIOL is

The name of your medicine is HEMANGIOL. The active ingredient is propranolol. Propranolol belongs to a group of medicines known as beta-blockers.

What it is used for

This medicine is used to treat a disease called haemangioma. A haemangioma is a collection of extra blood vessels that have formed a lump in or under the skin. Haemangioma can be superficial or deep. It is sometimes called 'strawberry mark' because the surface of a haemangioma looks a bit like a strawberry.

Hemangiol is started in infants aged 5 weeks to 5 months, when:

- the localisation and/or extend of the lesions are life- or function threatening (might impair vital organs or senses such as vision or hearing);
- the haemangioma is ulcerated and painful, and/or does not respond to simple wound care measures;
- there is a risk of permanent scars or disfigurement.

2 What you need to know before your child receives HEMANGIOL

Do not give HEMANGIOL

If your child:

- is born prematurely and he/she has not reached the corrected age of 5 weeks (the corrected age being the age a premature baby would be if he/she had been born on their due date).
- is allergic to propranolol or any of the other ingredients of this medicine (listed in section 6). An allergic reaction can include a rash, itching or shortness of breath.
- has asthma or history of breathing difficulties.

- has a slow heart rate for his/her age. Please check with your doctor if you are not sure.
- has a heart problem (such as disorders of the heart rhythm and heart failure).
- has very low blood pressure.
- has circulation problems which make the toes and fingers numb and pale.
- is prone to low blood sugar level.
- has a high blood pressure caused by a tumour on the adrenal gland. This is called 'phaeochromocytoma'.

If you are breastfeeding your child, and if you are taking medications that must not be used with HEMANGIOL (see “If you are breastfeeding your child” and “Other medicines and HEMANGIOL”) **do not give** this medicine to your child.

Warnings and precautions

Before your child receives HEMANGIOL, tell your doctor:

- If your child has problems with his/her liver or kidneys. This medicine will not be recommended in case of liver or kidneys impairment.
- If your child has ever had an allergic reaction. An allergic reaction can include a rash, itching or shortness of breath.
- If your child has psoriasis (a skin condition that produces red, dry plaques of thickened skin), as this medicine may worsen the symptoms of this condition.
- If your child has diabetes: in this case, your child’s blood sugar level should be measured more frequently.
- If your child has a PHACE syndrome (a condition combining haemangioma and vascular abnormalities including cerebral blood vessels), as this medicine may increase the risk of cerebral stroke.

Important signs to look after administration of HEMANGIOL

Risk of hypotension and bradycardia (low heart rate)

HEMANGIOL can decrease blood pressure (hypotension) and heart rate (bradycardia). This is why your child will be kept under close clinical and heart rate monitoring for 2 hours after the first dose or after a dose increase. Then, your doctor will regularly examine your child during treatment.

Call your doctor right away if your child has any signs such as fatigue, coldness, pallor, bluish-coloured skin, or fainting while taking HEMANGIOL.

Risks of hypoglycaemia

This medicine can mask the warning signs of hypoglycaemia (also known as low blood sugar level), especially if the baby is fasting, vomiting or in case of overdose. These signs may be:

- Minor: pallor, tiredness, sweating, shaking, palpitations, anxiety, hunger, difficulty waking up.
- Major: excessive sleeping, difficulty responding, poor feeding, decrease in body temperature, convulsions (fits), brief pauses in breathing, loss of consciousness.

To avoid risks of hypoglycaemia, your child must be fed regularly during treatment. If your child is not eating, develops another illness or is vomiting, it is recommended to skip the dose. DO NOT GIVE HEMANGIOL TO YOUR CHILD UNTIL HE HAS BEEN CORRECTLY FED AGAIN.

If your child has any signs of hypoglycaemia while taking HEMANGIOL, give if possible oral liquid containing sugar and, if symptoms persist, call your doctor right away or go directly to hospital.

Risks of bronchospasm

Stop treatment and contact your doctor immediately if after giving HEMANGIOL to your child you observe the following symptoms suggestive of a bronchospasm (temporary restriction of the bronchial tubes that leads to difficulty breathing): cough, quick or difficult breathing or wheezing, associated or not with a bluish-coloured skin:.

Risk of hyperkalemia

HEMANGIOL may increase potassium blood level (hyperkalemia) in case of large ulcerated haemangioma. In this case, your child's blood potassium level should be measured.

If your child should undergo a general anaesthesia

Tell the your doctor that he/she is taking HEMANGIOL. This is because your child can get low blood pressure if given certain anaesthetics while taking this medicine (see "Other medicines and HEMANGIOL"). HEMANGIOL might need to be discontinued at least 48h before the anaesthesia.

If you are breastfeeding your child

- Tell your doctor before giving this medicine.
- Do not give this medicine to your child if you are taking medications that must not be used with HEMANGIOL (see "Other medicines and HEMANGIOL").

Other medicines and HEMANGIOL

- Tell your doctor, pharmacist or nurse if you are giving, have recently given or might give any other medicines to your child. This is because HEMANGIOL can change the way other medicines work, and some medicines can have an effect on the way HEMANGIOL works.
- Moreover, if you are breastfeeding your child, it is important to tell your doctor, pharmacist or nurse which medicines you are yourself taking, as they may pass into your breast-milk and interfere with the treatment of your child. Your doctor will advise you on whether you need to stop breastfeeding or not.

In particular, in case you are breastfeeding, tell your doctor or pharmacist if you are or if your child is taking:

- Medicines for diabetes,
- Medicines for heart and blood vessels problems such as uneven heart beats, chest pain or angina, high blood pressure, heart failure,
- Medicines to treat anxiety and depression as well as more serious mental health problems, and epilepsy,
- Medicines to treat tuberculosis,
- Medicines to treat pain and inflammation,
- Medicines used to lower lipids in the blood,
- Medicines used for anaesthesia.

If you have any further questions, ask your doctor or pharmacist.

3 How HEMANGIOL is given

The treatment of your child has been initiated by a physician who has expertise in the diagnosis, treatment and management of infantile haemangioma.

Always give this medicine to your child exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Never change the dose you are giving to your child yourself. Every increase in dose or any dose adjustment to your baby's weight must be done by your doctor.

Dose

- Dosing is based on baby's weight.
- The starting dose is 1 mg/kg/day, in two divided doses (0.5 mg/kg, one in the morning and one in late afternoon), with a time interval of at least 9 hours between two intakes.
- The recommended dose is 3 mg/kg/day in two divided doses of 1.5 mg/kg, reached gradually with weekly increases under medical supervision (1 mg/kg/day the first week, then 2 mg/kg/day for the second week and then 3 mg/kg/day thereafter until end of the treatment).

How to give HEMANGIOL to your child

- The medicine is to be given during or straight after a feed.
- The dose should always be measured using the oral syringe supplied with the bottle.
- Give HEMANGIOL directly into your child's mouth using the oral syringe supplied with the bottle. If necessary, you may mix the product with a small quantity of baby-milk or age-adapted apple and/or orange fruit juice, and give it to your child in a baby bottle. Do not mix the medicine with a full bottle of milk or juice.

For children weighing up to 5 kg you may mix the dose 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 15 mL).

Use the mixture within 2 hours of preparation.

- Feed your child regularly to avoid prolonged fast.
- If your child is not eating or is vomiting it is recommended to skip the dose.
- If your child spits up a dose or if you are uncertain whether he/she got all of the medicine, do not give another dose, just wait until the next scheduled dose.
- 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 your child.

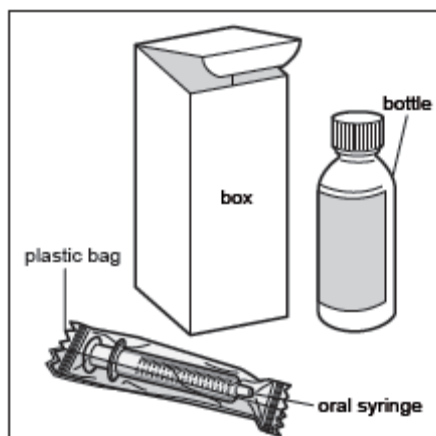
Instructions for use:

• **Step 1. Remove the items from the box**

The carton contains the following items that you will need to administer the medicine:

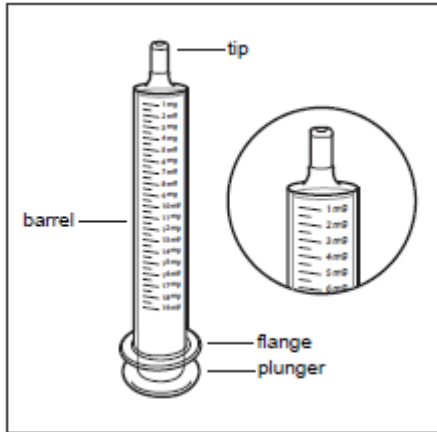
- The glass bottle containing 120 mL propranolol oral solution
- The oral syringe graduated in mg provided with this medicine

Remove the bottle and oral syringe from the box and remove the syringe from the plastic bag.



• **Step 2. Check the dose**

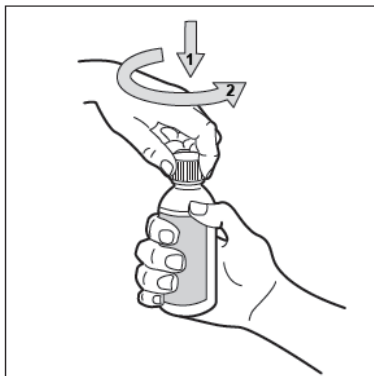
Check the HEMANGIOL dose in milligrams (mg) as prescribed by your doctor. Locate this number on the oral syringe.



- **Step 3. Open the bottle**

The bottle comes with a child-proof cap. Here is how to open it: push down the plastic cap while turning the cap counter-clockwise (to the left).

Do not shake the bottle before use.

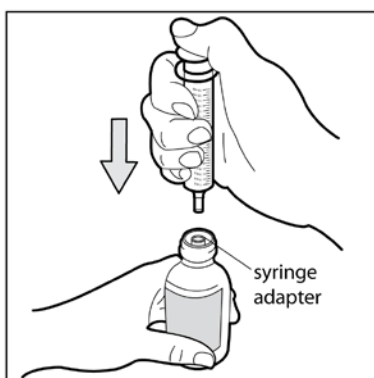


- **Step 4. Insert the syringe**

Insert tip of the oral syringe into the upright bottle and push the plunger all the way down.

Do not remove the syringe adapter from the neck of the bottle.

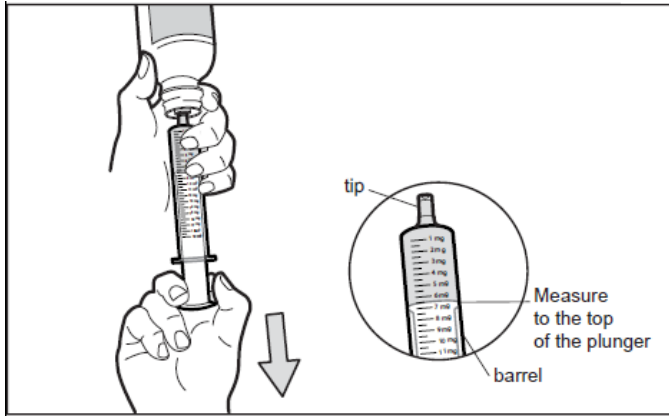
Only use the oral syringe that is supplied with the medicine to measure and administer the dose. Do not use a spoon or any other dispensing device.



- **Step 5: Remove the dose**

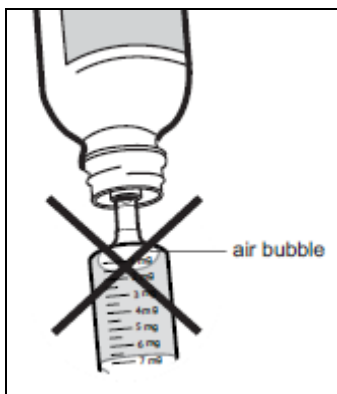
With the oral syringe in place, turn the bottle upside down.

Pull the plunger of the syringe up to the number of mg you need.



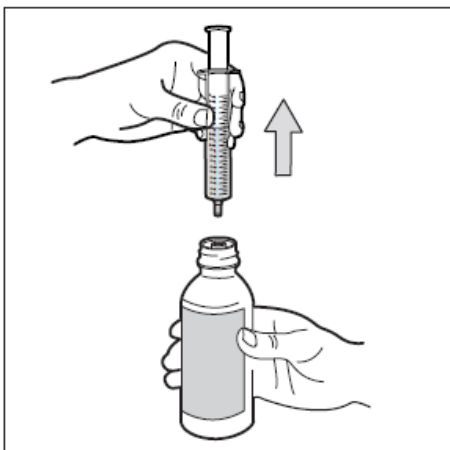
- **Step 6: Check for air bubbles**

If you see air bubbles in the syringe, hold the syringe upright, push the plunger upwards just far enough to completely push out any large air bubbles and then readjust to the dose prescribed by your doctor.



- **Step 7. Remove the syringe**

Turn bottle upright and remove the entire syringe from the bottle. Be careful, do not push the plunger in during this step.



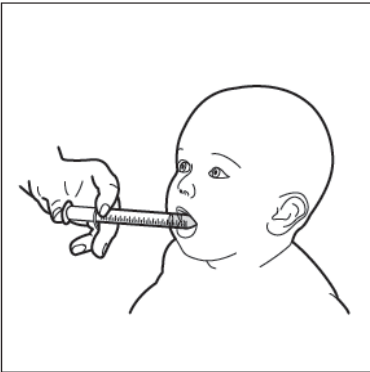
- **Step 8. Close the bottle.**

Replace the plastic cap on the bottle by turning it clock-wise (to the right).



- **Step 9. Give HEMANGIOL to your child**

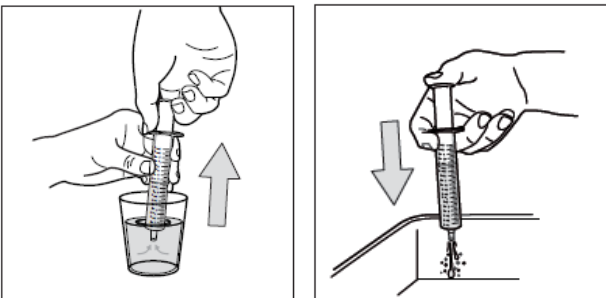
Insert the syringe into your baby's mouth and place it against the inside of the cheek. Now you can slowly squirt HEMANGIOL from the syringe directly into your baby's mouth. Do not lie the child down immediately after the administration.



- **Step 10: Clean the syringe.**

Do not dismantle the syringe. Rinse the empty syringe after each use into a glass of clean water:

- 1- Take a glass of clean water
- 2- Pull the plunger in
- 3- Discard the water into your sink
- 4- **Repeat this cleaning process 3 times.**



Do not use any soap or alcohol based product to clean. Wipe the outside dry.

Do not put the syringe through a sterilizer or dishwasher.

Store the bottle and the syringe together in the carton until next use in a safe place where your child can't see or reach it. Discard the syringe once the bottle is finished.

If you give to your child more HEMANGIOL than you should

If you have given to your child more HEMANGIOL than you should, please consult your doctor immediately.

If you forget to give HEMANGIOL to your child

Do not give a double dose to make up for a forgotten dose. Continue the treatment at the usual frequency: one dose in the morning and one in the late afternoon.

If you stop giving HEMANGIOL to your child

HEMANGIOL may be stopped at once at the end of the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

4 Possible side effects

Important warning signs of potential side effects such as low blood pressure, low heart rate, low blood sugar level, and bronchospasm should be looked after following administration of HEMANGIOL. Please refer to section 2 of this leaflet.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)

- Bronchitis (inflammation of the bronchi),
- Sleep disorders (insomnia, poor quality of sleep and difficulties to wake-up),
- Diarrhoea and vomiting.

Common side effects (may affect up to 1 in 10 people)

- Bronchospasm (breathing difficulties),
- Bronchiolitis (inflammation of small bronchi with breathing difficulties and wheeze in the chest, associated with cough and fever),
- Decreased blood pressure.
- Decreased appetite,
- Agitation, nightmares, irritability,
- Somnolence,
- Cold extremities,
- Constipation, abdominal pain,
- Erythema (skin redness),

Uncommon side effects (may affect up to 1 in 100 people)

- Heart conduction or rhythm disorders (slow or uneven heart beats),
- Urticaria (allergic reaction of the skin), alopecia (loss of hair),
- Decreased blood sugar levels,
- Reduction of the number of white blood cells.

The frequency of the following side effects is not known (frequency cannot be estimated from the available data)

- Convulsions (fits) linked to hypoglycaemia (abnormally low blood sugar levels),
- Bradycardia (abnormally low heart rate),
- Low blood pressure,
- Very low levels of white blood cells that fight infection
- Circulation problems which make the toes and fingers numb and pale

- Elevated level of potassium in the blood

Reporting of side effects

If your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store HEMANGIOL

Keep this medicine out of the sight and reach of children.

The medicine must not be frozen. Keep the bottle in the outer carton in order to protect from light.

Store the oral syringe with the bottle in the outer carton between each use.

Do not use this medicine after the expiry date which is stated on the bottle. The expiry date refers to the last day of that month.

After first opening, the medicine should be used within 2 months.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 Contents of the pack and other information

What HEMANGIOL contains

- The active substance is propranolol. Each ml contains 4.28 mg of propranolol hydrochloride equivalent to 3.75 mg of propranolol.
- The other ingredients are hydroxyethylcellulose, sodium saccharin, strawberry flavour (contains propylene glycol), vanilla flavour (contains propylene glycol), citric acid monohydrate, purified water.

What HEMANGIOL looks like and contents of the pack

- HEMANGIOL is a clear, colourless to slightly yellow oral solution, with a fruity odour.
- It is supplied in a 120-mL amber glass bottle, with a child resistant screw-cap. Box of 1 bottle.
- An oral polypropylene syringe graduated in mg of propranolol, is provided with each bottle.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

PIERRE FABRE DERMATOLOGIE

45 Place Abel Gance

92100 BOULOGNE

FRANCE

Manufacturer

FARMEA

10 rue Bouché Thomas

ZAC Sud d'Orgemont

49000 ANGERS

FRANCE

Or

PIERRE FABRE MEDICAMENT PRODUCTION
Site SIMAPHAC, Zone Industrielle de Chateaurenard
45220 CHATEAURENARD
FRANCE

Or

PIERRE FABRE MEDICAMENT PRODUCTION
Site PROGIPHARM, Rue du Lycée
45500 GIEN
FRANCE

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.