HIGHLIGHTS OF PRESCRIBING INFORMATION
HEMANGEOL® (propranolol hydrochloride) oral solution

These highlights do not include all the information needed to use HEMANGEOL safely and effectively. See full prescribing information for HEMANGEOL.

Initial U.S. Approval: 1967

……INDICATIONS AND USAGE……..……

HEMANGEOL oral solution is a beta-adrenergic blocker indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy. (1)

……DOSAGE AND ADMINISTRATION……..

- Initiate treatment at ages 5 weeks to 5 months. (2)
- Starting dose is 0.15 mL/kg (0.6 mg/kg) twice daily. After 1 week, increase dose to 0.3 mL/kg (1.1 mg/kg) twice daily. After 2 weeks, increase to a maintenance dose of 0.4 mL/kg (1.7 mg/kg) twice daily. (2)
- Administer doses at least 9 hours apart during or after feeding. (2)
- Readjust dose for changes in the child's weight. (2)
- Monitor heart rate and blood pressure for 2 hours after the first dose or increasing dose. (2)

……..…DOSAGE FORMS AND STRENGTHS…….……

Oral solution: 4.28 mg/mL propranolol hydrochloride (3)

……CONTRAINDICATIONS…….....……

- Premature infants with corrected age <5 weeks (4)
- Infants weighing less than 2 kg (4)
- Known hypersensitivity to propranolol or excipients (4)
- Asthma or history of bronchospasm (4, 5.3, 6, 10, 17)
- Bradycardia (<80 beats per minute), greater than first degree heartblock, decompensated heart failure (4, 5.2, 5.4, 10, 17)
- Blood pressure <50/30 mmHg (4, 5.2, 10, 17)
- Pheochromocytoma (4)

……..……..…WARNINGS AND PRECAUTIONS…...……

- Hypoglycemia: Administer during or after feeding. Do not use in patients who are not able to feed or are vomiting (4, 5.1, 6, 10, 17).
- Bradycardia and hypotension (4, 5.2, 17)
- Bronchospasm: Avoid use in patients with asthma or lower respiratory infection. (4, 5.3, 6, 10, 17)
- Increased risk of stroke in PHACE syndrome (5.5)

……..……ADVERSE REACTIONS…….……

The most common adverse reactions to HEMANGEOL (occurring ≥ 10% of patients) were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. at 1-855-224-0233 or FDA at 1-800- FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HEMANGEOL oral solution contains the beta-adrenergic blocker propranolol hydrochloride and is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

2 DOSAGE AND ADMINISTRATION

Initiate treatment at ages 5 weeks to 5 months.

The recommended starting dose of HEMANGEOL is 0.15 mL/kg (0.6 mg/kg) (see Table 1) twice daily, taken at least 9 hours apart. After 1 week, increase the daily dose to 0.3 mL/kg (1.1 mg/kg) twice daily. After 2 weeks of treatment, increase the dose to 0.4 mL/kg (1.7 mg/kg) twice daily and maintain this for 6 months. Readjust the dose periodically as the child's weight increases.

To reduce the risk of hypoglycemia, administer HEMANGEOL orally during or right after a feeding. Skip the dose if the child is not eating or is vomiting *[see Warnings and Precautions (5.1)]*.

Monitor heart rate and blood pressure for 2 hours after HEMANGEOL initiation or dose increases *[see Warnings and Precautions (5.2)]*.

If hemangiomas recur, treatment may be re-initiated *[see Clinical Studies (14)]*.

HEMANGEOL is supplied with an oral dosing syringe for administration. Administration directly into the child's mouth is recommended. Nevertheless, if necessary, the product may be diluted in a small quantity of milk or fruit juice, given in a baby's bottle.

Table 1. Dose Titration According to Weight

	Week 1	Week 2	Week 3 (maintenance)
Weight (kg)	**Volume administered twice a day**	**Volume administered twice a day**	**Volume administered twice a day**
2 to <2.5	0.3 mL	0.6 mL	0.8 mL
2.5 to <3	0.4 mL	0.8 mL	1 mL
3 to <3.5	0.5 mL	0.9 mL	1.2 mL
3.5 to <4	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	0.7 mL	1.4 mL	1.8 mL
5 to <5.5	0.8 mL	1.5 mL	2 mL
5.5 to <6	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	1 mL	2 mL	2.6 mL
7 to <7.5	1.1 mL	2.1 mL	2.8 mL
7.5 to <8	1.1 mL	2.3 mL	3 mL
8 to <8.5	1.2 mL	2.4 mL	3.2 mL
8.5 to <9	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 mL	4 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

3 DOSAGE FORMS AND STRENGTHS

Oral solution: 4.28 mg/mL propranolol hydrochloride.

Alcohol-, paraben- and sugar-free.

4 CONTRAINDICATIONS

HEMANGEOL is contraindicated in the following conditions:

- Premature infants with corrected age < 5 weeks
- Infants weighing less than 2 kg
- Known hypersensitivity to propranolol or any of the excipients *[see Description (11)]*
- Asthma or history of bronchospasm
- Heart rate <80 beats per minute, greater than first degree heart block, or decompensated heart failure
- Blood pressure <50/30 mmHg
- Pheochromocytoma

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

HEMANGEOL prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations and sweating. HEMANGEOL can cause hypoglycemia, at any time during treatment. Risk is increased during a fasting period (e.g., poor oral food intake, infection, vomiting) or when glucose demands are increased (e.g., cold, stress, infections). Withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. Discontinue HEMANGEOL if hypoglycemia develops and treat appropriately

Concomitant treatment with corticosteroids may increase the risk of hypoglycemia *[see Drug Interactions (7)]*.

5.2 Bradycardia and Hypotension

HEMANGEOL may cause or worsen bradycardia or hypotension. In the studies of HEMANGEOL for infantile hemangioma the mean decrease in heart rate was about 7 bpm with little effect on blood pressure. Monitor heart rate and blood pressure after treatment initiation or increase in dose. Discontinue treatment if severe (<80 beats per minute) or symptomatic bradycardia or hypotension (systolic blood pressure <50 mmHg) occurs.

5.3 Bronchospasm

HEMANGEOL can cause bronchospasm; do not use in patients with asthma or a history of bronchospasm. Interrupt treatment in the event of a lower respiratory tract infection associated with dyspnea and wheezing.

5.4 Cardiac Failure

Sympathetic stimulation supports circulatory function in patients with congestive heart failure, beta blockade may precipitate more severe failure.

5.5 Increased Risk of Stroke in PHACE Syndrome

By dropping blood pressure, HEMANGEOL may increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies.

Investigate infants with large facial infantile hemangioma for potential arteriopathy associated with PHACE syndrome prior to HEMANGEOL therapy.

5.6 Hypersensitivity

Beta-blockers will interfere with epinephrine used to treat serious anaphylaxis.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypoglycemia and related events, like hypoglycemic seizure *[see Warnings and Precautions (5.1)]*.
- Bronchospasm *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in clinical practice.

Clinical Trials Experience with HEMANGEOL in Infants with proliferating infantile hemangioma
In clinical trials for proliferating infantile hemangioma, the most frequently reported adverse reactions (>10%) in infants treated with HEMANGEOL were sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhea, and vomiting. Adverse reactions led to treatment discontinuation in fewer than 2% of treated patients.

Overall, 479 patients in the pooled safety population were exposed to study drug in the clinical study program (456 in placebo-controlled trials). A total of 424 patients were treated with HEMANGEOL at doses 1.2 mg/kg/day or 3.4 mg/kg/day for 3 or 6 months. Of these, 63% of patients were aged 91-150 days and 37% were aged 35-90 days at randomization.

The following table lists according to the dosage the most common adverse reactions (treatment-emergent adverse events with an incidence at least 3% greater on one of the two doses than on placebo).

Table 2. Treatment-emergent adverse events occurring at least 3% more often on HEMANGEOL than on placebo

Reaction	Placebo N=236	HEMANGEOL 1.2 mg/kg/day N=200	HEMANGEOL 3.4 mg/kg/day N=224
Sleep disorder	5.9%	17.5%	16.1%
Bronchitis	4.7	8.0	13.4
Peripheral coldness	0.4	8.0	6.7
Agitation	2.1	8.5	4.5
Diarrhea	1.3	4.5	6.3
Somnolence	0.4	5.0	0.9
Nightmare	1.7	2.0	6.3
Irritability	1.3	5.5	1.3
Decreased appetite	0.4	2.5	3.6
Abdominal pain	0.4	3.5	0.4

The following adverse events have been observed during clinical studies, with an incidence of less than 1%:
Cardiac disorders: Second degree atrioventricular heart block, in a patient with underlying conduction disorder, required definitive treatment discontinuation *[see Warnings and Precautions (5.4)]*.
Skin and subcutaneous tissue disorders: Urticaria, alopecia
Investigations: Decreased blood glucose, decreased heart rate

Compassionate Use Program
More than 600 infants received HEMANGEOL in a compassionate use program (CUP). Mean age at treatment initiation was 3.6 months. Mean dose of HEMANGEOL was 2.2 mg/kg/day and mean treatment duration was 7.1 months.

The adverse reactions reported in the CUP were similar to the ADRs observed during clinical trials but some were more severe.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of propranolol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are as follows:

Blood and lymphatic system disorders: Agranulocytosis

Psychiatric disorders: Hallucination

Skin and subcutaneous tissues disorders: Purpura, dermatitis psoriasiform

7 DRUG INTERACTIONS

In the absence of specific studies in children, the drug interactions with propranolol are those known in adults. Consider both the infant's medications and those of a nursing mother.

Pharmacokinetic drug interactions

Impact of co-administered drugs on propranolol: CYP2D6, CYP1A2 or CYP2C19 inhibitors increase propranolol plasma concentration. CYP1A2 inducers (phenytoin, phenobarbital) or CYP2C19 inducers (rifampin) decrease propranolol plasma concentration when co-administered.

Pharmacodynamic drug interactions

Corticosteroids: Patients on corticosteroids may be at increased risk of hypoglycemia because of loss of the counter-regulatory cortisol response; monitor patients for signs of hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Of 460 infants with proliferating infantile hemangioma requiring systemic therapy who were treated with HEMANGEOL starting at 5 weeks to 5 months of age, 60% had complete or nearly complete resolution of their hemangioma at Week 24 *[see Clinical Studies (14)]*.

Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

8.6 Hepatic Impairment

There is no experience in infants with hepatic impairment.

8.7 Renal Impairment

There is no experience in infants with renal impairment.

10 OVERDOSAGE

Few cases of propranolol overdose were reported. For a single intake, the maximum dose was 20 mg/kg. Symptomatic cases featured hypotension, hypoglycemic seizure, and restlessness/euphory/insomnia; for most cases, propranolol was maintained or reintroduced.

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.

Support and treatment: Place the patient on a cardiac monitor, and monitor 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 IV fluid. Isoproterenol and aminophylline may be used for bronchospasm.

Propranolol is not dialyzable.

11 DESCRIPTION

HEMANGEOL is an oral solution of propranolol that is alcohol free, paraben free and sugar free. Each mL of HEMANGEOL contains 4.28 mg of propranolol hydrochloride, USP equivalent to 3.75 mg of propranolol.

Propranolol hydrochloride is a synthetic beta-adrenergic receptor blocking agent chemically described as (2RS)1-[(1-methylethyl)amino]-3-(naphthalene-1-yloxy)-propan-2-ol hydrochloride. Its structural formula is shown in Figure 1:

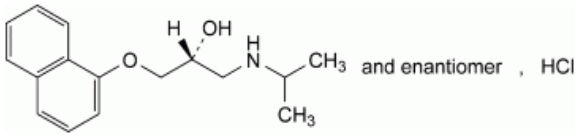

Figure 1. Propranolol HCl structure

Molecular formula: $C_{16}H_{21}NO_2$-HCl

Propranolol hydrochloride is a stable, white, crystalline solid with a molecular weight of 295.8. It is readily soluble in water and ethanol.

HEMANGEOL contains the following inactive ingredients: strawberry/vanilla flavorings, hydroxyethylcellulose, saccharin sodium, citric acid monohydrate, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of HEMANGEOL's effects on infantile hemangiomas is not well understood.

12.2 Pharmacodynamics

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol selectively blocks beta-adrenergic receptors, leaving alpha-adrenergic responses intact. There are two well-characterized subtypes of beta receptors (beta1 and beta2); propranolol interacts with both subtypes equally.

Beta1-adrenergic receptors are found primarily in the heart. Blockade of cardiac beta1-adrenergic receptors leads to a decrease in the activity of both normal and ectopic pacemaker cells and a decrease in A-V nodal conduction velocity. Blockade of cardiac beta1-adrenergic receptors also decreases the myocardial force of contraction and may provoke cardiac decompensation in patients with minimal cardiac reserve.

Beta2-adrenergic receptors are found predominantly in smooth muscle-vascular, bronchial, gastrointestinal and genitourinary. Blockade of these receptors results in constriction. Propranolol's beta-blocking effects are attributable to its S(-) enantiomer.

Pharmacodynamic drug interactions

Alpha blockers: Co-administration of beta-blockers with alpha blockers (prazosin) has been associated with prolongation of first dose hypotension and syncope.

Antidepressants: The hypotensive effect of MAO inhibitors and tricyclic antidepressants is exacerbated when administered with beta-blockers.

Nonsteroidal anti-inflammatory drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs) may attenuate the antihypertensive effect of beta-adrenoreceptor blocking agents. Monitor blood pressure.

12.3 Pharmacokinetics

Adults

Absorption: 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.

Distribution: 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.

Propranolol is extensively metabolized with most metabolites appearing in the urine.

Metabolism: 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 (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life.

Elimination: 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.

Infants

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 hemangioma. 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.

Sex

There is no known dependence of pharmacokinetics of propranolol by sex in infants.

Race

There is little information on dependence of pharmacokinetics of propranolol by race in infants.

A study conducted in 12 Caucasian and 13 African-American adult male subjects taking propranolol, showed that at steady state, the clearance of R(+)- and S(-)-propranolol were about 76% and 53% higher in African-Americans than in Caucasians, respectively.

Chinese adult subjects had a greater proportion (18% to 45% higher) of unbound propranolol in plasma compared to Caucasians, which was associated with a lower plasma concentration of alpha1 acid glycoprotein.

Drug Interaction Studies

Impact of propranolol on co-administered drugs: The effect of propranolol on plasma concentration of co-administered drug is presented in the table below.

Table 3. Effect of propranolol on co-administered drugs

Co-administered drug	Effect on plasma concentration of co-administered drug
Amide anesthetics (lidocaine, bupivacaine, mepivacaine)	Increase
Warfarin	Increase
Propafenone	Increase > 200 %
Nifedipine	Increase 80 %
Verapamil	No change
Pravastatin, lovastatin	Decrease 20%
Fluvastatin	No change
Zolmitriptan	Increase 60 %
Rizatriptan	Increase 80 %
Thioridazine	Increase 370 %
Diazepam	Increase
Oxazepam, triazolam, lorazepam, alprazolam	No change
Theophylline	Increase 70 %

Impact of co-administered drugs on propranolol: The effect of co-administered drugs on propranolol plasma concentration is presented in the table below.

Table 4. Effect of co-administered drugs on propranolol

Co-administered drug	Effect on propranolol plasma concentration
CYP2D6, CYP1A2 or CYP2C19 inhibitors	Increase
CYP1A2 or CYP2C19 inducers	Decrease
Quinidine	Increase > 200 %
Nisoldipine	Increase 50 %
Nicardipine	Increase 80 %
Chlorpromazine	Increase 70 %
Cimetidine	Increase 50 %
Cholestyramine, colestipol	Decrease 50 %
Alcohol	Increase (acute use), decrease (chronic use)
Diazepam	No change
Verapamil	No change
Metoclopramide	No change
Ranitidine	No change
Lansoprazole	No change
Omeprazole	No change
Propafenone	Increase 200 %
Aluminum hydroxide	Decrease 50 %

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies of mice and rats fed propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is about 3 and 7 times, respectively, the MRHD of 3.4 mg/kg/day propranolol hydrochloride in children.

Based on differing results from bacterial reverse mutation (Ames) tests performed by different laboratories, there is equivocal evidence for mutagenicity in one strain (*S. typhimurium* strain TA 1538).

In a study in which both male and female rats were exposed to propranolol hydrochloride via diet at concentrations of up to 0.05% (about 50 mg/kg or less than the MRHD of 640 mg propranolol hydrochloride in adults) started from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. The potential effects of propranolol hydrochloride on fertility of juvenile rats were evaluated following daily oral administration from post-natal Day 4 (PND 4) to PND 21 at dose-levels of 0, 11.4, 22.8 or 45.6 mg/kg/day. No propranolol related effects on reproductive parameters or reproductive development were observed up to the highest dose level of 45.6 mg/kg/day, a dose that represents a systemic exposure of 3 times that seen in children at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

This study in juvenile rats with propranolol hydrochloride described above was intended to cover the period of development corresponding to infancy, childhood and adolescence. Neurologic effects including hypoactivity and delayed air righting reflex, increased germinal centers of lymph nodes, and increased white blood cells and lymphocytes were seen at a propranolol hydrochloride dose 45.6 mg/kg/day that represents a systemic exposure of 3 times that seen in children at the MRHD. Body weights were transiently decreased, and transient decreases in urine volume were associated with higher incidences of minimal renal cysts and dilation of kidney tubules at doses about equal to the MRHD in children.

14 CLINICAL STUDIES

A randomized, double-blind study in 460 infants, aged 35 days to 5 months at inclusion, with proliferating infantile hemangiomas (IH) requiring systemic therapy (excluding life-threatening IH, function-threatening IH, and ulcerated IH with pain and lack of response to simple wound care measures) compared four regimens of HEMANGEOL (1.2 or 3.4 mg/kg/day in twice daily divided doses for 3 or 6 months; N=99-103 per group) to placebo (N=55). Clinical efficacy was evaluated by counting complete or nearly complete resolution of the target hemangioma, which was evaluated by blinded centralized independent assessments of photographs at Week 24 compared to baseline.

Demographic patient characteristics and hemangioma characteristics were similar among the five regimens. For the whole population, 29% were male, 37% were in the lower age group (35-90 days), and 72% were Caucasian. Overall, 70% had a target hemangioma on the head, most commonly cheek (13%) and forehead (11%).

The main reason for treatment discontinuation was the treatment inefficacy, which happened in 58% of patients randomized to placebo, 25-30% of patients randomized to HEMANGEOL for 3 months (mainly after the switch to placebo), and 7-9% of patients randomized to HEMANGEOL for 6 months.

Overall, 2 out of 55 patients (4%) in the placebo arm and 61 out of 101 patients (60%) on HEMANGEOL 3.4 mg/kg/day for 6 months had complete or nearly complete resolution of their hemangioma at Week 24 ($p < 0.0001$).

There were no significant differences in response by age (35-90 days / 91-150 days), sex, or hemangioma site. There were too few non-Caucasians to assess differences in effects by race.

Of patients on HEMANGEOL 3.4 mg/kg/day for 6 months who were considered successes, 10% required retreatment for recurrence of hemangiomas.

A second uncontrolled study in 23 patients with proliferating IH included function-threatening IH, IH in certain anatomic locations that often leave permanent scars or deformity, large facial IH, smaller IH in exposed areas, severe ulcerated IH, pedunculated IH. Target lesions resolved in 36% of patients by 3 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HEMANGEOL is supplied as an oral solution. Each 1 mL contains 4.28 mg propranolol. HEMANGEOL is supplied in a carton containing one bottle with syringe adapter and one 5-mL oral dosing syringe.

NDC 71863-132-12	Bottle 120 mL
NDC 71863-132-50	Bottle 50 mL

16.2 Storage and Handling

Store at 25ºC (77ºF); excursions permitted from 15º to 30ºC (59º to 86ºF). [See USP Controlled Room Temperature.]
Do not freeze.
Do not shake the bottle before use.
Dispense in original container with enclosed oral dosing syringe.
The product can be kept for 2 months after first opening.

See instructions for using enclosed oral dosing syringe.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Patient advice
Advise parents or caregivers to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instructions for using oral dosing syringe
Instruct parents or caregivers on use of the oral dosing syringe.

Risk of hypoglycemia
Inform parents or caregivers that there is a risk of hypoglycemia while on HEMANGEOL. Hypoglycemia can occur at any time during treatment. Instruct caregivers to skip dosing in patients who are fasting (e.g., poor oral food intake, infection, vomiting), or when glucose demands are increased (e.g., cold, stress, infections). Instruct parents or caregivers how to recognize the signs of hypoglycemia. Tell them to discontinue HEMANGEOL if hypoglycemia develops and call their health care provider immediately or take the child to the emergency room *[see Warnings and Precautions 5.1]*

Cardiovascular risks
Advise parents or caregivers that there is a potential risk for bradycardia, aggravation of pre-existing conduction disorders, and hypotension associated with the use of HEMANGEOL. Instruct them to contact their healthcare provider in case of fatigue, pallor, slow or uneven heart beats, peripheral coldness or fainting.

Respiratory risks
Inform parents or caregivers that HEMANGEOL carries risk of bronchospasm or exacerbation of lower respiratory tract infections. Instruct them to contact their healthcare provider or go to the nearest hospital emergency room if their child has breathing problems or wheezing during treatment with HEMANGEOL.

Other risks
Inform parents or caregivers that changes in sleep patterns may occur during HEMANGEOL therapy.

Ask parents or caregivers to tell you all the medications they are administering to their child including prescription and over the counter medicines, vitamins, and herbal supplements. Ask breastfeeding mothers to tell you all the medications they are currently taking, as these may pass into the milk.

Manufactured for:

Eton Pharmaceuticals, Inc., Deer Park, IL 60010

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