Press Release
For Immediate Release

Pierre Fabre publishes new data on dosing errors with generic propranolol for the treatment of infantile hemangiomas

Parsippany, NJ; April 24, 2017 – Pierre Fabre announced the publication of data from an institutional review board-approved survey comparing the propensity for dispensing and dosing calculation errors of HEMANGEOL® (propranolol hydrochloride oral solution 4.28 mg/mL) versus other propranolol hydrochloride oral solutions (4 mg/mL and 8 mg/mL) (also known as generic* propranolol hydrochloride) during the treatment of infantile hemangiomas. The survey of 220 pediatric dermatologists and other physicians who treat infantile hemangioma found that they were significantly more likely to commit an error with the other formulations of propranolol versus HEMANGEOL. The findings were published in the Journal of the American Academy of Dermatology.

HEMANGEOL is the first and only FDA-approved drug indicated for the treatment of infantile hemangiomas. Other formulations of propranolol have not been studied or demonstrated safety and efficacy for this orphan indication.

"Medication errors injure more than one million people in the United States every year,"[i] said study author Dr. Elaine Siegfried, Department of Dermatology, Saint Louis University. "Liquid medications prescribed to infants have particularly complex dosing requirements due to weight-based dosing and metric system conversions. This study is meant to raise awareness around the potential of errors, and especially the need to educate parents administering propranolol at home versus in a hospital-setting."

Infantile hemangioma is the most common benign tumor in infants, but in some cases may be associated with serious complications and life-long disfigurement. It is estimated to affect between 4-10% of infants.[ii] The risk of disfigurement depends on several factors including the location, size, shape and growth-rate of the tumor.[iii] Even tumors as small as one centimeter can lead to permanent, stigmatizing skin changes if they affect the infant's eyes, nose and mouth.[ii] As many as 25% of infants with a hemangioma will experience a related complication[iv] and approximately 10% will experience serious or life-threatening complications that may have been preventable.[v]

In the email-based survey of 220 physicians, about 90 percent reported prescribing other propranolol formulations and 58 percent reported prescribing HEMANGEOL. Additionally, the survey found that:[vi]

- 30 percent reported at least one dose calculation error with other propranolol formulations compared to 11 percent with HEMANGEOL (p=0.00012)
    - A subset analysis of pediatric dermatologists with experience writing 10-100 prescriptions found similar results, with 31 reporting dose calculation errors with other propranolol formulations compared to 10 percent for HEMANGEOL
- 18 percent reported dispensing errors with other propranolol formulations, having received an incorrect, higher concentration from a pharmacy (p<0.0001)

    - Because HEMANGEOL is available in a single concentration and distributed by a single specialty pharmacy, dispensing errors are not possible.
- A total of 41 percent reported either a dosing or calculation error with other propranolol formulations ($p<0.0001$)

"Early intervention is required to prevent long term complications from hemangioma.[vii] Pierre Fabre not only conducted the pivotal studies necessary to support approval of HEMANGEOL, but exclusively distributes HEMANGEOL through a single specialty pharmacy to verify dose calculations and provide support to caregivers. Additionally, HEMANGEOL packaging includes a dosing table and syringe to help avoid over- or under-dosing." said Jean-Jacques Voisard, dermatologist and General Manager of Pierre Fabre Dermatologie.

*Other propranolol hydrochloride formulations are not therapeutically equivalent to HEMANGEOL® (propranolol hydrochloride)

About HEMANGEOL®
HEMANGEOL formulation was specifically developed for the use in pediatric populations following the guidelines of health regulatory agencies. HEMANGEOL was studied in infants five weeks to five months old (at therapy initiation) with a proliferative infantile hemangioma requiring systemic treatment in a randomized, double blind placebo controlled, multi-dose and multi-center adaptive phase II/III trial, which compared four propranolol hydrochloride treatment protocols (1.2 or 3.4 mg/kg/day for 3 or 6 months) versus placebo. The treatment protocol of 3.4 mg/kg/day dose for the duration of six months had a 60.4% success rate versus 3.6% in the placebo group ($p< 0.0001$) reaching the primary endpoint of complete or nearly-complete resolution of the target hemangioma. About 10% of patients needed to be retreated after stopping the treatment.

About Pierre Fabre
Pierre Fabre is a French private pharmaceutical and dermo-cosmetic company founded in 1962 by Mr. Pierre Fabre. The company is structured around two divisions: Pierre Fabre Pharmaceuticals (ethics, oncology, consumer health care) and Pierre Fabre Dermo-Cosmétique (dermatology, dermo-cosmetics). In dermo-cosmetics, its portfolio of 9 brands includes global market-leader, Eau Thermale Avène. Pierre Fabre employs some 13,000 people worldwide and owns subsidiaries in 43 countries. Pierre Fabre allocates about 16% of its pharmaceuticals sales to R&D with a focus on 4 therapeutic areas: oncology, dermatology, central nervous system and consumer health care.

Pierre Fabre has a unique shareholding structure that guarantees its continuity and independence. The majority shareholder is the Pierre Fabre Foundation, which is a government-recognized public-interest organization. It has also developed its employee stock ownership plan, and employees thus form the second-largest group of shareholders. This structure is unique in France and is aimed at ensuring the long-term stability of the company's capital.

Indication
Hemangeol® (propranolol hydrochloride) oral solution is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

IMPORTANT SAFETY INFORMATION
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;

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; and pheochromocytoma.

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 in children, especially when they are not feeding regularly or are vomiting; withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. If a child has clinical signs of hypoglycemia, parents should discontinue HEMANGEOL and call their health care provider immediately or take the child to the emergency room. Concomitant treatment with corticosteroids may increase the risks of hypoglycemia.

HEMANGEOL may cause or worsen bradycardia or hypotension. 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.

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.

HEMANGEOL may worsen circulatory function in patients with congestive heart failure or 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. Hemangeol will interfere with epinephrine used to treat serious anaphylaxis.

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

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[i] US Food and Drug Administration website. Medication error reports. Available at: http://www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm080629.htm.
[ii] Frieden IJ, et al. *Pediatr Dermatol.* 2005;22:383-406.
[iii] Haggstrom AN, et al. *Arch Dermatol.* 2012;148:197-202.
[iv] Haggstrom AN, et al. *Pediatrics*. 2006;118:882-887.
[v] Stiles J, et al. *Exp Ther Med.* 2012;4:594-604.
[vi] Kurta A, et al. J Am Acad Dermatol. 2017;76:999-1000.
[vii] Craig LM, Alster TS. *Dermatol Surg.* 2013;39:1137-1146.