

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 21, 2014

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Division of Risk Management (DRISK)

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Drug Name(s): (b) (4) (Propranolol Hydrochloride)

Therapeutic Class: Beta-Blocker

Dosage and Route: Propranolol 3.75 mg/mL, 3 mg/kg/day, Oral Solution

Application Type/Number: NDA/205-410

Submission Number: Supporting Document 1 (Sequence 0000)

Applicant/sponsor: Pierre Fabre Pharmaceuticals, Inc

OSE RCM #: 2012-1383

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1 INTRODUCTION

The purpose of this review is to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) for (b) (4) (propranolol oral solution). The New Drug Application (NDA 205-410) was submitted by Pierre Fabre Pharmaceuticals, Inc. on May 17, 2013 and is under review in the Division of Cardiovascular and Renal Products (DCRP) for the treatment of proliferating infantile hemangioma in patients aged five weeks to five months.

1.1 BACKGROUND

Propranolol is a non-selective beta-adrenergic receptor blocking agent. Propranolol blocks beta receptor sites and causes a decrease in the chronotropic, inotropic, and vasodilation responses to beta-adrenergic stimulation. Propranolol has been in clinical use since the 1960s. The main indication is as an antihypertensive treatment. However, it is also approved for the treatment of angina pectoris, atrial fibrillation, myocardial infarction, migraine, essential tremor, hypertrophic subaortic stenosis and pheochromocytoma. Off label uses of propranolol are often reported, including treatment of post-traumatic stress disorder and infantile hemangiomas.^{i,ii}

Treatment of infantile hemangiomas with propranolol was reported for the first time in 2008 and was described as providing a marked effect.ⁱⁱⁱ Since then, efficacy has been documented in the literature in various publications. However, propranolol has not been formulated for pediatric use and is not approved for pediatric use.

Infantile hemangiomas (IH) are the most common vascular tumors of childhood. They are benign and affect approximately 4% of Caucasian infants.ⁱⁱ These tumors are characterized by endothelial cell proliferation. They exhibit a characteristic evolution with early rapid growth (proliferation) followed by a stabilization period and a slow spontaneous involution. The lesions are usually not detectable at birth but appear during the first four to six weeks of life. Most IH have an uncomplicated clinical course; however, some are associated with complications that can be life-threatening (e.g. respiratory failure in airway IH) or function-threatening (anisometropia, astigmatism, and amblyopia in periocular IH and feeding difficulties in lip IH).

There are no approved treatments for IH in the U.S. Corticosteroids, interferon alpha and vincristine are used as treatments for IH. These treatments have shown varying responses and have significant side-effect profiles.

The Sponsor notes that propranolol has been used successfully to treat IH since 2008 and is becoming a first line, off label use for this condition. They propose this oral solution to meet an unmet need for infants with IH. The proposed strength to be marketed is 3.75 mg/mL. This strength covers the expected weight range of infants to be treated (2 to 12 kg) at the concentration of 3 mg/kg/day; this results in an intake volume of less than 5 mL.

The submission did not contain a REMS proposal.

1.2 REGULATORY HISTORY

The Sponsor states that they designed the pivotal clinical study (Study 201) to be consistent with recommendations made by both the FDA and the European Medicines

Agency. This included extensive scientific advice discussions, a Special Protocol Assessment (SPA) in the US, and a Pediatric Investigation Plan (PIP) in Europe. The SPA was designed to identify appropriate dosing and duration as well as show superiority over placebo.

Important regulatory meetings were as follows:

- The Sponsor had a Pre-IND meeting on January 30, 2009
- A Type A meeting was held on November 10, 2009
- A Type C teleconference was held on May 21, 2009
- The Pre-NDA meeting was held on April 24, 2012
- A Type C meeting to discuss topline results was held on December 7, 2012

The meetings listed above primarily focused on study population, design, statistics, treatment duration and other aspects of the clinical program. However, at the Type C meeting in December 2012, the Sponsor explained that the following risks had been identified during the clinical program: bradycardia, hypotension, hypoglycemia and bronchospasm. They proposed a REMS consisting of:

- A communication plan for health care professionals to ensure good use of treatment, with prescriber and professional organization letters and REMS website with voluntary web-based training on the disease and on the monitoring of the treatment
- A Medication Guide to help patients' parents prevent serious adverse events.
- Assessment plan taking into account the FDA's recommendations laid down in the Draft Guidance for Industry on the Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications (2009).

The Agency responded that there was insufficient information to determine whether a REMS would be necessary to ensure that the benefits of the drug outweigh the risks, and if necessary, what the required elements should be. As mentioned, the NDA did not contain a REMS proposal. There was a proposed Patient Package Insert (PPI).

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The materials that informed this review were:

- Pierre Fabre Pharmaceuticals, Inc. *Clinical Overview* received on May 17, 2013
- Pierre Fabre Pharmaceuticals, Inc. *Summary of Clinical Safety* received on May 17, 2013
- Pierre Fabre Pharmaceuticals, Inc. *Draft Labeling* (including PPI) received on May 17, 2013
- Pierre Fabre Pharmaceuticals, Inc. *Correspondence Regarding Meetings* received on May 17, 2013

3 OVERVIEW OF CLINICAL PROGRAM

The primary analysis contained pooled data from two clinical studies that were conducted in the target population of infants with proliferating IHs. These studies were:

- Study V00400SB 102 (Study 102): An open-label, repeated-dose study to determine the steady-state pharmacokinetic profile of propranolol in 23 infants.

Efficacy results

Results showed that treatment with propranolol for 12 weeks resulted in a rapid improvement (within 7-14 days) in all patients. Resolution of the target hemangioma was seen as early as one month. Resolution was observed in 8 out of 22 patients (36.4%) by three months.

- Study V00400 SB 201 (Study 201—this was the SPA study): A pivotal, Phase II/III, randomized, placebo-controlled clinical trial to select the best of four regimens of propranolol to demonstrate its efficacy against placebo. There were a total of 460 patients randomized to treatment; 456 received at least one dose of study treatment (401/propranolol and 55/placebo). The clinical benefit was evaluated by a prospectively defined binary endpoint, success/failure. Success was defined as complete or nearly complete resolution of the target hemangioma, which was evaluated by blinded centralized independent assessments of photographs at Week 24, in the absence of premature treatment discontinuation. The treatment regimen 3 mg/kg/day for 6 months had been selected at the end of the phase 2 part of the study.

Efficacy results

Overall, 2 out of 55 patients (3.6%) in the placebo arm and 61 out of 101 patients (60.4%) in the 3 mg/kg/d, for 6 months propranolol arm presented a complete or nearly complete resolution of their hemangioma at week 24.

4 SAFETY DATABASE

4.1 OVERVIEW

The safety database in the U.S. clinical program consisted of patients from the two supportive studies; there were a total of 424 patients treated with (b) (4) and 236 treated with placebo. In the clinical program, the most common adverse events (AEs) (occurring $\geq 10\%$ of patients treated with (b) (4) were bronchitis (10.8% versus 4.7% in placebo) and sleep disorders (16.7% vs. 5.9%). Other AEs seen more often in patients treated with (b) (4) include diarrhea (5.4% vs. 1.3%) and peripheral coldness (7.3% vs. 0.4%).

4.2 SERIOUS ADVERSE EVENTS (SAEs)

No death was reported during the study treatment period. Thirty-one SAEs were reported in the clinical program in patients treated with [REDACTED] (b) (4). The most common SAEs were: condition aggravated, drug ineffective and bronchiolitis (each reported in 3 patients), and bronchitis (2 patients). All other SAEs were reported in a single patient each. Four of these were considered related to the drug by the investigator. There was one SAE of second degree block where a pre-existing cardiologic disease was identified later. This SAE did not require corrective treatment. One SAE of IH ulceration occurred; treatment was discontinued. There was one expected SAE which was a case of bradycardia described below. In addition, there was a case that the Sponsor considered related to the study drug of obstructive bronchitis in the 3 mg/kg/day 3 months regimen; treatment was temporarily discontinued in this case.

4.3 ADVERSE EVENTS OF SPECIAL INTEREST

AEs of special interest with this product are bradycardia, hypotension, bronchospasm and hypoglycemia. Please see Dr. Khin U's review for a full review of safety and these AEs. He has discussed the findings from the clinical program, the Sponsor's Compassionate Use Program (CUP) (additional 159 treated patients) in France and also findings from scientific publications.

CARDIAC EFFECTS: Bradycardia and Hypotension

There was one patient that had a SAE of bradycardia during the uptitration period. The drug was discontinued and the bradycardia resolved. There was one other AE of bradycardia; this was a mild case that occurred weeks after starting treatment. No intervention was needed.

There were three patients reported with hypotension during uptitration and three after uptitration. None were SAEs. None of the patients presented with symptoms or had drug discontinuation.

The Sponsor's proposed label [REDACTED] (b) (4)

[REDACTED] Current labeling has some of the same contraindications; there are contraindications to specific cardiac conditions (cardiogenic shock and sinus bradycardia) and asthma. Hypotension is not contraindicated in current labeling.

The Sponsor proposes Warning and Precaution for patients that develop severe bradycardia or hypotension. They also propose that patients are monitored after treatment initiation and after uptitrations for a period of two hours, as they were in the clinical trials.

Reviewer comment: The cardiac effects of propranolol are well known, expected adverse events. Post approval it is expected that [REDACTED] (b) (4) treatment titration will occur in a

monitored setting (i.e. physician's office). Therefore, bradycardia and hypotension can be monitored at each dosage change in order to mitigate this risk. The Sponsor's proposed labeling provides appropriate warnings and recommendations to mitigate this risk.

Bronchospasm

Two patients treated with (b) (4) had bronchospasm and two patients that received placebo had bronchospasm. None were SAEs.

Consistent with current labeling, (b) (4) is proposed to be contraindicated in patients with asthma or bronchospasm. Due to the risk of bronchospasm, patients are to discontinue treatment if they develop a respiratory disorder with dyspnea and wheezing; this is described under Warnings and Precautions.

Reviewer comment: Bronchospasm and related risks such as bronchiolitis will cause signs and symptoms in infants that their caregivers are likely to notice and immediately seek treatment. Therefore, additional risk mitigation beyond labeling is not necessary to address this risk.

Hypoglycemia

There were two patients that had hypoglycemia during the uptitration period. Both cases were mild and there was recovery without changing the study drug. There were no reported symptoms. One of these patients had concurrent gastroenteritis. Dr. U notes that in the CUP, there were also four cases where two patients had seizures. Both cases occurred when the patients were not fed before administration of (b) (4). No blood glucose levels were documented for these cases. Additional cases have also been documented in the scientific literature. In a case report and review of the literature of patients treated with propranolol for hemangioma, three cases of symptomatic hypoglycemia were described. Twenty-one documented cases were also found on review.^{iv}

The Sponsor (b) (4). They also propose for Warnings and Precautions that propranolol masks the warning signs of hypoglycemia and that it can aggravate hypoglycemia. Current approved labeling includes a warning for patients with diabetes under the title "Diabetes and Hypoglycemia." This warning emphasizes that propranolol can prevent the signs and symptoms of acute hypoglycemia. Additionally, this section states that propranolol, "particularly when given to infants and children, diabetic or not, has been associated with hypoglycemia." Of note, the current label also states that propranolol is not approved for use in children.

Additionally, the Sponsor proposed a Patient Package Insert (PPI) which follows their proposed label in the NDA submission, titled *Patient Information*. The PPI emphasizes the cardiovascular and hypoglycemic effects of (b) (4). The first risk discussed is the

cardiovascular related risks (hypotension and bradycardia). The second risk is hypoglycemia. It lists preventative measures that the caregiver can follow to avoid hypoglycemia and also how to correct it.

Reviewer comment: Due to the potential seriousness of the AE's associated with undetected hypoglycemia in the indicated patient population (infants 5 weeks to 5 months), additional risk mitigation beyond the sponsor's proposed labeling is necessary and is discussed more below.

5 DISCUSSION OF THE RISK OF HYPOGLYCEMIA

Caregivers of patients in this study, and likely in other studies documented in the scientific literature, were informed of the risk of hypoglycemia and how to prevent it (feeding before the dose and interrupting treatment in the case of no feeds/vomiting). Though hypoglycemia was seen in the clinical program, the incidence was low and there were no related SAEs. However, incidents resulting in seizures were reported in both the CUP program and in literature. This event can lead to seizures, coma or death if not recognized and corrected. Current approved labeling describes hypoglycemia as well, emphasizing that this risk has been seen particularly in association with treatment in infants and children.

Infants, in particular, are prone to conditions that may keep them from feeding properly, such as reflux or even an upper respiratory tract infection. Although older children may complain of dizziness or lightheadedness, infants cannot communicate the symptoms of hypoglycemia. Signs are also difficult to detect in this age group (i.e. pallor, sleepiness). Furthermore, infants have lower glycogen stores.^{iv} Due to the risk of hypoglycemia and the potential serious adverse events resulting from unrecognized hypoglycemia in infants (i.e. seizures, coma or death), continuing the education of caregivers after initiation is important if (b) (4) is approved.

The proposed PPI explains the risk of hypoglycemia and gives detailed information to caregivers on how to prevent this risk. However, pharmacies are not required to distribute PPI when the medication is dispensed. A Medication Guide, however, is required to be distributed with the medication at each dispensing. The Agency can require a Medication Guide when one or more of these situations exist:

- 1) The drug product is one for which patient labeling could help prevent serious adverse effects.
- 2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.
- 3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

In the case of hypoglycemia, the Medication Guide falls under *1) The drug product is one for which patient labeling could help prevent serious adverse effects*. Though the actual SAEs were not seen in the clinical program (there were no hospitalizations or deaths

related to hypoglycemia), this risk and possible significant outcomes can be prevented. The paper document will be a resource for caregivers that will be administering a medication to their small infant and it will be given directly to the caregiver from the pharmacy upon picking up the medication. This document would be a valuable resource that reinforces the counseling that takes place at the physician's office. Since it will be given to the caregiver with every prescription pick up, it will serve as a reminder about the importance of prevention weeks or months after the initial counseling takes place.

Although the Sponsor's proposed label addressed hypoglycemia, Section 17 Patient Counseling, only briefly addressed this risk and provided no details on prevention or correction. The only details were those provided in the PPI. Therefore, additional information for the provider to counsel the caregiver was warranted, including the importance of regular feeding and need to hold the medication if the infant is not feeding.

6 CONCLUSION/RECOMMENDATIONS

In the review to date, no AEs of particular concern or preclinical safety signals have been identified that cannot be discussed and communicated through approved labeling.

DRISK recommends that the Patient Package Insert, proposed by the Sponsor, be converted to a Medication Guide. This Medication Guide should focus on the risk of hypoglycemia, prevention and corrective measures. This should be the first risk discussed in the Medication Guide. In addition, further counseling recommendations were discussed with the Division and incorporated into Section 17 Patient Counseling.

In conclusion, risk mitigation measures beyond approved labeling which includes a Medication Guide are not warranted for (b) (4).

Should DCRP raise concerns with risks discussed in this review, or identify additional risks associated with (b) (4) warranting more extensive risk mitigation or a formal REMS, please send a consult to DRISK.

This memo serves as the primary DRISK review for (b) (4) under NDA 205-410. Please notify DRISK if you have any questions.

ⁱ Brunet A, et al. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research* 2008; 42: 503-6.

ⁱⁱ Hogeling, M. Propranolol for Infantile Hemangiomas: A Review. *Current Dermatology Reports* 2012; 101:469-474.

ⁱⁱⁱ Leute-Labreze, C. et al Propranolol for Severe Hemangiomas of Infancy *NEJM* 2008: 358; 2649-51.

^{iv} Holland, K.E. et al. Hypoglycemia in Children Taking Propranolol for the Treatment of Infantile Hemangioma. *Arch Dermatol.* 2010; 146: 775-778.

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