CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205410Orig1s000

OTHER REVIEW(S)

RPM Overview – AP action
NDA 205-410
Hemangeol (propranolol HCl) Oral Solution
4.28 mg/mL

Sponsor:	Pierre-Fabre Pharmaceuticals, Inc.
Classification:	Standard
Letter Date:	May 17, 2013
User Fee Receipt Date:	May 17, 2013
User Fee Goal Date:	March 17, 2014

Background
Pierre Fabre Pharmaceuticals, Inc. submitted this 505(b)(2) NDA for Hemangeol (propranolol HCl) Oral Solution, 4.28 mg/mL for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy. The intended population includes infants aged 5 weeks to 5 months. The reference listed drug (RLD) that is the basis for this NDA submission is Inderal (propranolol HCl), NDA 16-418. Hemangeol was granted an orphan designation for the proposed indication on September 5, 2008 (Orphan Designation #08-2667).

This NDA included an assessment of published non-clinical studies and refers to the RLD, Inderal, to fulfill the requirements for non-clinical studies.

In support of approval, the clinical development is based on three clinical studies (conducted under IND 104,390):

- Two pharmacokinetic studies (Study V00400 SB 101 2A in healthy adults and Study V00400 SB 102 in infants with IH)
- One pivotal Phase II/III study (Study V00400 SB 201)

Reviews

Division Director's Review
In his 3-5-14 review, Dr. Stockbridge recommended approval.

Deputy Director for Safety's Memo
In her 2-10-14 memo, Dr. Mary Ross Southworth wrote the following:

> I believe it is appropriate to require a Medication Guide for this product. Hypoglycemia is a known adverse event associated with propranolol use; hypoglycemic seizures, rare and serious, have been reported. Appropriate feeding and dosing instructions will help mitigate that risk. The Medication Guide (dispensed from the pharmacy along with the drug) would serve as an important tool to help reinforce and remind caregivers about these measures.
>
> Because of the lack of data to support a signal for an effect of propranolol on later neurocognitive development and study design factors (poor retention, lack of a control group), I do not recommend that the sponsor be required to perform a post marketing study to evaluate the impact of use of propranolol in infants on neurological and cognitive development.

Cross-Discipline Team Leader Review
In his 2-7-14 review, Dr. U recommended approval. See also his 3-7-14 addendum, which states: "This addendum to CDTL review describes new information since filing of the CDTL review. The new information does not change the approval recommendation of the NDA."

Clinical Review
In his 12-20-13 review, Dr. U wrote the following:

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is approval (§21 CFR 314.110) pending the sponsor's response to agree to the suggested changes in the proposed labeling.

Statistical Review
In her 1-13-14 review, Dr. Chen wrote the following:

5.2 CONCLUSIONS AND RECOMMENDATIONS
Study V00400 SB 201 appeared to support the propranolol's efficacy for both 3 mg and 1 mg 6 months regimens. However, there were differential dropout rates between the placebo and the study doses and between different regions/countries (most placebo dropouts were from Western Europe and France). While it can be argued that a much higher dropout rate in the placebo group might lend an additional assurance for propranolol's efficacy, that the placebo group had a much higher dropout rate and dropped out early and most placebo dropouts took propranolol as the prohibited medications after dropping out might have yielded a bias in favor of propranolol. Hence the strength of evidence for the propranolol efficacy is probably overstated by the nominal p-value based on a number of the reviewer's sensitivity analyses.

Clinical Pharmacology Review
In her 1-18-14 review, Dr. Menon-Andersen wrote the following:

1.1. Recommendations
The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 205410. The NDA can be approved from a clinical pharmacology perspective provided agreement is reached with the applicant on labeling.

Pharmacology Review
In her 8-7-13 review, Dr. Yang indicated that the NDA was approvable. See review in DAARTS.

ONDQA Biopharmaceutics Review
In her 1-7-14 review, Dr. Riviere wrote the following:

In conclusion, based on the overall supportive scientific evidence, the bridging between the proposed and RLD propranolol products is adequately justified and acceptable. From the Biopharmaceutics standpoint, (b) (4) (propranolol) Oral Solution, 3.75 mg/mL is recommended for approval.

Product Quality Microbiology Review
In her 12-5-13 review, Dr. Pfeiler wrote the following:

The microbial limits specifications for Propanolol are acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

CMC Review
In his 3-7-14 review, Dr. Shiromani wrote the following:

The following Summary Report from the Office of Compliance was received on 07-Feb-2014, with an 'Acceptable' overall recommendation. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 31-Dec-2013.

See also CMC review dated 12-31-13.

Environmental Assessment
The sponsor claimed a categorical exclusion from the requirement to provide an environmental assessment (EA) under 21 CFR Part 25.31(b), which was found to be acceptable. See CMC review.

EER Report (Manufacturing Site Inspections)
The Office of Compliance issued an Overall Recommendation of "Acceptable" on 3-7-14; see CMC review.

Advisory Committee (AC) Meeting
This NDA was not referred to an FDA Advisory Committee because the drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

Safety Update
See Dr. U's 12-20-13 Clinical review.

Debarment Certification
A correctly worded Debarment Certification with authorized signature was submitted on 5-17-13.

Financial Disclosure
See section **3.3 Financial Disclosures** of Dr. U's 12-20-13 Clinical review.

Office of Scientific Investigations
The Clinical Inspection Summary dated 12-9-13 states the following:

> **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**
> This clinical inspection summary contains the results of an ORA/OSI conducted domestic inspection as well as the results of two EMA conducted foreign inspections in France and Peru and an inspection conducted in France of the sponsor IRPF. The inspection of Dr. Friedlander's site was unremarkable. One of the most significant issues identified at the foreign sites and the sponsor was not a GCP violation, but rather a failure to precisely identify in the protocol how the IH lesions should be measured.
> Since the majority if sites (48/54) used lesion size + induration, an overall effect on the study seems unlikely, but the review division may wish to compare the two sets of sites, since the six sites using size alone might underestimate lesion size at enrollment compared to the remainder of sites. Failure to classify some cases of Grade 4 neutropenia as "Clinically Significant" may have resulted in missing AEs/SAEs; when this issue was examined by the sponsor, the number appears to be relatively small (approximately three subjects). Failure to collect subject diaries has the potential to underestimate AEs, but the diaries were intended to be used at subject visits as a tool. Despite minor GCP violations noted, the data may be considered adequate and may be used in support of the pending application.

Pediatrics
Hemangeol was granted an orphan designation for the proposed indication on September 5, 2008 (Orphan Designation #08-2667). Because this drug product for this indication has an orphan drug designation, the application is **exempt** from the requirement under PREA to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients.

Labeling
The original submission contains proposed draft labeling for the package insert (PI) in PLR format, a Patient PI (PPI), Instructions for Use (IFU), and carton and container labeling.

OPDP completed a review of the draft PI and carton and container labeling on 1-27-14 (see review in DARRTS).

Due to the risk of hypoglycemia, the proposed PPI was converted to a Medication Guide (MG). DMPP and OPDP completed a collaborative review of the MG and IFU on 1-27-14. The appended IFU incorporates DMPP and DMEPA comments (see review in DARRTS).

Dr. Sachs of PMHT provided suggested language for subsection **8.4 Pediatric Use** of the draft PI on 3-11-14.

SEALD completed the End-of-Cycle labeling review of the draft PI on 3-11-4.

Labeling comments on the draft PI, MG, and IFU were sent to the applicant on 2-13-14, 3-4-14, 3-13-14 and 3-14-14. The sponsor agreed to the Division's labeling edits on 3-14-14.

DMEPA found the revised carton and container labeling submitted on 3-4-14 to be acceptable in their review dated 3-10-14. DMEPA previously reviewed the proposed labels and labeling in their reviews dated 11-27-13, 1-15-14, 2-21-14, and 2-26-14.

Proprietary Name Review
DMEPA initially found the originally proposed proprietary name "(b) (4)" acceptable in their reviews dated 8-7-13 (submitted under the NDA) and 10-5-12 (submitted under IND 104,390). Subsequent to these reviews, (b) (4) (b) (4). As a result of this change to the (b) (4), DMEPA found the name "(b) (4)" unacceptable. A teleconference was held between DMEPA and the applicant on 3-3-14 to communicate the unacceptability of the name "(b) (4)." As a result, the applicant submitted a new name "Hemangeol" which was found to be acceptable by DMEPA in their review dated 2-14-14.

OSE Review (DRISK)
In her 1-21-14 review, Dr. Dunn wrote the following:

> **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.

Safety Discussion
A Safety Discussion was held as part of the Wrap-up Meeting on 1-29-14 with OSE. Based on the discussion, Susan Lu of OSE/DPV-1 indicated that no additional measures beyond routine pharmacovigilance appear to be warranted.

User Fee
This application is covered by the following user fee exemption: Orphan exception under Section 736(a)(1)(F) of the Federal Food, Drug and Cosmetic Act. (User Fee ID# PD3013308)

505(b)(2) Clearance
Per a 2-27-14 email from Mary Ann Holovac of the OND IO, this NDA is cleared for action from a 505(b)(2) perspective.

RPM Summary
An Approval (AP) Letter based on the agreed-upon labeling text will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
3-14-14

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUYNH M NGUYEN
03/14/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**HEMANGEOL™ (propranolol hydrochloride oral solution)**
Applicant	Pierre Fabre Pharmaceuticals, Inc.
Application/Supplement Number	NDA 205410
Type of Application	Original
Indication(s)	treatment of proliferating infantile hemangioma requiring systemic therapy
Office/Division	ODE I/DCRP
Division Project Manager	Quynh Nguyen
Date FDA Received Application	May 17, 2013
Goal Date	March 17, 2014
Date PI Received by SEALD	March 10, 2014
SEALD Review Date	March 11, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The margin between the columns is less than 1/2 inch.*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The headings for DFS and AR and not centered.*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *The reference is missing for the last bulleted statement in W&P.*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Selected Requirements of Prescribing Information

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *The current PI has an EPC of "beta-blocker" while the eList has the EPC "beta-Adrenergic Blocker" for propranolol. If the proposed EPC is appropriate, please ask Paul Brown to update eLIST or if the eList EPC is correct, please revise the PI accordingly.*

Dosage Forms and Strengths in Highlights

N/A

20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *In HL, the term "bradycardia" is used prior to "(<80 beats per minute)"; the term "bradycardia" is missing from the FPI and the term "heart rate <80 beats per minute" is used. If the review division believes including "bradycardia" would be helpful to prescribers, then consider also including it in the FPI; otherwise, recommend removing "bradycardia" from HL and stating "heart rate <80 beats per minute". Of note, W&P 5.2 references a heart rate < 80 bpm as "severe bradycardia".*

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Subsection 8.4 Pediatric Use is missing and is required by regulation (see 21 CFR 201.57(c)(9)(iv)). Also, subsection 12.4 should be "Microbiology", when applicable; recommend revising so current "12.4 Drug Interactions" is revised to "12.6 Drug Interactions".*

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment: *The second cross-reference in Section 2 D&A is missing the outer bracket. The word "see" in the cross-references under 5.1and 6.1 is not italicized.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *This statement has been modified, but is acceptable if agreed to by the review division.*

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

Comment: *Note: the word "voluntarily" is misspelled in the FPI as "voluntary".*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH A DONOHOE
03/11/2014

ERIC R BRODSKY
03/11/2014
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

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 Label and Labeling Memo

Date:	March 7, 2014
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	Lisa Khosla, PharmD, MHA Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Hemangeol (propranolol hydrochloride) Oral Solution 4.28 mg/ml
Application Type/Number:	NDA 205410
Applicant/sponsor:	Pierre-Fabre Dermatologie
OSE RCM #:	2014-307-2

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised labels and labeling for Hemangeol, NDA 205410, received March 3, 2014 from the Applicant (Appendices A and B). DMEPA previously reviewed the proposed labels and labeling under OSE Review #2013-1353, 2013-2863, 2014-307 and 2014-307-1 dated November 27, 2013, January 15, 2014, February 19, 2014 and February 26, 2014 respectively.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling received March 3, 2014. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-1353, 2013-2863, 2014-307 and 2014-307-1 dated November 27, 2013, January 15, 2014, February 19, 2014 and February 26, 2014 respectively.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised labels and labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn at 301-796- 2084.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JACQUELINE E SHEPPARD
03/10/2014

LISA V KHOSLA
03/10/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 205-410	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Hemangeol Established/Proper Name: propranolol HCl Dosage Form: Oral Solution Strengths: 4.28 mg/mL		
Applicant: Pierre Fabre Pharmaceuticals, Inc.		
Date of Receipt: 5-17-13		
PDUFA Goal Date: 3-17-14	Action Goal Date (if different):	
RPM: Quynh Nguyen, PharmD, RAC		
Proposed Indication(s): For the treatment of proliferating infantile hemangioma requiring systemic therapy.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Nonclinical toxicology
NDA 16-418, Inderal (propranolol hydrochloride) Tablets	FDA's previous finding of safety and effectiveness (e.g., clinical and nonclinical)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This application relies on FDA's finding of safety for NDA 16-418 for Inderal (propranolol) tablets to support its nonclinical development program. As Inderal is no longer marketed, the applicant used Pliva*'s 40 mg. propranolol tablet, approved under ANDA 71974, to bridge to Inderal. Pliva's 80 mg tablet (ANDA 71976) is identified in the Orange Book as the reference standard for propranolol tablets.

Bridging to Inderal was established using a 2-step approach:

- An *in vivo* bioavailability comparison between the 505(b)(2) product and a French-approved propranolol tablet (Avlocardyl®) that demonstrated in 12 healthy adults comparable bioavailability profiles between the two formulations.
- An in vitro dissolution test that demonstrated the equivalence of dissolution profiles of Avlocardyl® and Pliva's propranolol 40 mg tablets (approved under ANDA 71974).

*Barr Pharmaceuticals, Inc. was acquired by Pliva in 2008.

Though the bridging approach is unusual from a regulatory perspective, a key factor in the acceptability of the approach is that the Division considered it to be appropriate from a scientific perspective.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Inderal (propranolol hydrochloride) Tablets

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Inderal (propranolol hydrochloride) Tablets	NDA 16-418	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

NDA 16-418/ Inderal (propranolol HCl) Tablets.

Note: the Orange Book currently lists the product as Rx but it has been confirmed that it is not in the marketplace and a safety/effectiveness relisting has been requested by the Orange Book staff.

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication and dosage form (oral solution).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(***Pharmaceutical alternatives*** *are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

Pharmaceutical alternatives: multiple extended release capsules, injectables, and immediate release tablets. Reference the OB for complete list.

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

QUYNH M NGUYEN
03/10/2014

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

Label and Labeling Memo

Date:	February 26, 2014
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	Lisa Khosla, PharmD, MHA Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Hemangeol (Propranolol Hydrochloride) Solution, 4.28 mg/ml
Application Type/Number:	NDA 205410
Applicant/sponsor:	Pierre-Fabre Dermatologie
OSE RCM #:	2014-307-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Hemangeol (propranolol hydrochloride), NDA 205410, received on February 25, 2014 from the Applicant (Appendices A and B). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed labels and labeling under OSE Review # 2013-1353 and 2013-2863 dated November 27, 2013 and January 15, 2014 under the proposed trade name (b) (4) and OSE Review # 2014-307 dated February 19, 2014 under the proposed trade name Hemangeol***.

2 MATERIALS REVIEWED

DMEPA reviewed the labels and labeling received on February 5, 2014. We compared the revised labels and labeling against our recommendations in OSE Review # 2013-1353, 2013- 2862 and 2014-307 dated November 27, 2013, January 15, 2014, and February 19, 2014 respectively, to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 RESULTS

A review of the revised labels and labeling determined that the Applicant addressed our previous recommendations. However, we note that the strength of the product was placed in between the established name and dosage form, which is not the customary presentation of the established name. Additionally, we note that the "Date of first opening" box is not as prominent as it was in previous labels and labeling submissions. We provide recommendations in section 4 to address these deficiencies.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the revised labels and labeling can be improved for safe use of the product and to increase prominence of important information.

Based on this review, DMEPA advises the recommendations below be implemented prior to approval of this NDA.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn at 301-796-2084.

4.1 COMMENTS TO THE APPLICANT

1. Ensure that the established name and dosage form is not separated by the presentation of strength as presented below.

   Hemangeol

   (propanolol hydrochloride) oral solution

   4.28 mg/mL

2. Use color to highlight “Date of first opening” box on the bottle label. This was previously done in other incarnations of the labels and labeling.

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/s/

JACQUELINE E SHEPPARD
02/26/2014

LISA V KHOSLA
02/26/2014

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

Label and Labeling Memo

Date:	February 19, 2014
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	Lisa Khosla, PharmD, MHA Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Hemangeol (Propranolol Hydrochloride) Solution, 4.28 mg/ml
Application Type/Number:	NDA 205410
Applicant/sponsor:	Pierre-Fabre Dermatologie
OSE RCM #:	2014-397

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1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Hemangeol (propranolol hydrochloride), NDA 205410, received on February 5, 2014 from the Applicant (Appendices A and B). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed labels and labeling under OSE Review # 2013-1353 and 2013-2863 dated November 27, 2013 and January 15, 2014 under the trade name (b) (4) ***

2 MATERIALS REVIEWED

DMEPA reviewed the labels and labeling received on February 5, 2014. We compared the revised labels and labeling against our recommendations in OSE Review # 2013-1353 and 2013-2863 dated November 27, 2013 and January 15, 2014, to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 RESULTS

A review of the revised labels and labeling determined that the Applicant addressed our previous recommendations. However, there are additional areas that can be improved from a medication error prospective. Since a Medication Guide is being requested for Hemangeol, the Applicant is responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to dispensers to provide a Medication Guide to each patient to whom the drug is dispensed. We provide this recommendation in Section 4.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the revised labels and labeling can be improved for safe use of the product.

Based on this review, DMEPA advises the recommendations below be implemented prior to approval of this NDA. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn at 301-796-2084.

4.1 COMMENTS TO THE APPLICANT

A. Revise container label and carton labeling with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton

- "Dispense the enclosed Medication Guide to each patient."
- "Dispense the accompanying Medication Guide to each patient."

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/s/

JACQUELINE E SHEPPARD
02/20/2014

LISA V KHOSLA
02/21/2014

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 10, 2014

From: Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products /CDER

To: File

Subject: Propranolol solution (NDA 205-410) for proliferating infantile hemangiomas: Need for Medication Guide and consideration for post-marketing study

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Propranolol solution (proposed tradename (b) (4) is currently under review for the treatment of proliferating infantile hemangiomas (IH). IH are benign vascular tumors which appear in some infants (~3-10%) during the first 4 to 6 weeks of life. Most are cosmetic in nature, but up to 24% of patients may experience complications (involvement of the eye, feeding difficulties, skin ulceration). There are no approved therapies for IH in the US.

Oral propranolol is approved in the US for the treatment of hypertension in adults; safety and effectiveness in pediatric patients have not been established. However, propranolol solution has been used off-label for treating hypertension (literature based dose recommendation: 0.5 to 1 mg/kg/d in 2 to 4 divided doses, increasing to a maximum of 8 mg/kg/d[1]).

Propranolol appears to be effective for treating IH[2]. The proposed dose is 0.6 mg/kg twice daily, titrated up to a maximum of 1.8 mg/kg twice daily. Known safety issues relate to its pharmacologic properties (bradycardia, hypotension, bronchospasm, and hypoglycemia). The purpose of this memo is to 1.) review the need for a Medication Guide and 2.) consider the evidence of propranolol's effect on neurocognitive development in growing children and evaluate the need for a required post-marketing study.

The risk of hypoglycemia and the need for a Medication Guide

[1] Anderson PO et al. Handbook of Clinical Drug Data 10th edition, 2002.
[2] U, K, Cross-DisciplineTeam Leader memo (draft), Version 1/29/2014.

Propranolol may precipitate hypoglycemia and mask some of its associated symptoms (tremor, tachycardia). Severe hypoglycemia has the potential to lead to seizures and coma. The current labeling for oral propranolol[3] lists "masked signs of hypoglycemia" as a Warning. The "Labor and Delivery" section of labeling lists hypoglycemia as an adverse event observed in neonates whose mother had received propranolol at the time of delivery.

As Dr. U states in his CDTL memo, no cases of clinically significant hypoglycemia were observed in the safety population receiving propranolol in the NDA, nor were detectable changes noted in blood glucose levels post-dosing. However, in a Compassionate Use Program (600 infants treated with propranolol for IH), 4 cases of hypoglycemia were observed; two of these patients experienced seizures—both reportedly related to a failure to give feeds prior to propranolol administration. Dr. U advises that the risk of hypoglycemia can be mitigated by "proper education of parents and caregivers on the importance of administering propranolol during or right after a feeding". The risk of hypoglycemia and recommendations regarding dose in relationship to feeding, holding the dose if the child is vomiting or not taking feeds, and when to seek medical care are appropriately included in the Warning section of the proposed label for this product.

Dr. Dunn (Division of Risk Management)[4] recommends that a Medication Guide, describing the risk of hypoglycemia, prevention and corrective measures, be included as part of labeling because *patient labeling could help prevent serious adverse effects* (one of the criteria under which FDA can require distribution of a Medication Guide with every prescription dispensed- 21 CFR part 208.1c). Dr. U is not in agreement with this recommendation because he believes the risk of hypoglycemia does not qualify as a serious adverse effect and the Medication Guide would detract from the physician's message about appropriate risk mitigation measures.

I believe it is appropriate to require a Medication Guide for this product. Hypoglycemia is a known adverse event associated with propranolol use; hypoglycemic seizures, rare and serious, have been reported. Appropriate feeding and dosing instructions will help mitigate that risk. The Medication Guide (dispensed from the pharmacy along with the drug) would serve as an important tool to help reinforce and remind caregivers about these measures.

Propranolol and neurocognitive development

Little information exists regarding the effects of propranolol, or other beta-blockers, on long term neurocognitive development when given to infants. The adrenergic system plays a role in memory storage and cognition[5,6,7], but an association between beta-blocker use and effects on cognition in developing animals is not well defined. In one study[8]

[3] NDA 21438, Innopran XL, drugs@fda, accessed February 6, 2014.
[4] Dunn, S, NDA 205410, REMS review, January 21, 2014.
[5] Liang KC, Juler RG, McGaugh JL, Brain Research 1986; 368:125-133.
[6] Liang KC, Bennett C, McGaugh JL, Behav Brain Res 1985; 15: 93-100.
[7] Chamberlain SR, Robbins TW. Journal of Psychopharmacology 2013; 27: 694-718.
[8] Hilakivi LA, et al. Early postnatal treatment with propranolol affects development of brain amines and behavior.

propranolol use in juvenile rats (< 20 days old, 5 to 10 mg/kg) lead to changes in some behaviors (more floating in a swim test, increase in voluntary alcohol consumption), but not others (response to auditory stimulation) compared to controls several months later.

There are little long term data describing long term effects in children whose mother received prenatal beta-blocker therapy. Most of the literature on the use of beta blockers in pregnancy suggest an adverse effect on fetal growth (intrauterine growth retardation)[9,10,11]. This risk is described in the current label for propranolol. An association between pre-natal use of beta blockers and effects on behavior/ neurologic development in subsequent children does not appear to be established.

Studies have examined the use of prenatal beta agonists (used as tocolytics) and effects on behavior in children. Delayed effects on cognition and behavior were observed[12] in a group of children whose mother received tocolytic therapy, compared to control. However, the use of tocolytic agent was not randomized and sometimes included non-beta agonist tocolytics; therefore it is hard to discern what is really a drug effect. One study[13] found no difference between a group of 6 year old children whose mothers received ritodrine as a tocolytic vs. a control group with regard to neurologic findings and general behavior, but noted that school performances were considered "less good" in the group that had been exposed to ritodrine. The quality of studies in this area limits the interpretation of the data.

I would not consider a signal for cognitive or behavioral effects related to prenatal or neonatal use of propranolol to be strong.

Dr. U has expressed concern with the lack of data on the long term neurological effects of acute or chronic beta blockade in children. He has proposed to have the sponsor create a registry which would follow up, over the next 5 to 7 years, children who were enrolled in studies 201 and 102 (about 55 placebo patients and 425 propranolol treated patients) and measure several developmental milestones. I have concerns regarding the interpretability of information that this registry would generate. First, the retention rate of subjects over the years would likely be low. Second, many of the subjects in the placebo arm crossed over to active treatment. Without an adequately sized control group, the usefulness of this registry data is limited. Dr. U also has proposed following all IH propranolol patients post approval to examine how the developmental milestones differ in the propranolol treated children compared to the standard national milestones in each region or country. Given the wide variation in how children develop (within and between each regions), I do not believe an open label registry would be able to reliably detect a propranolol effect on developmental milestones. Furthermore, requiring all propranolol treated subjects enter a (US) registry would require a restricted distribution system to ensure that patients were

[9] Rosenthal T, The effect of antihypertensive drugs on the fetus. J Human Hypertens 2002; 16: 293-98.
[10] Magee La et al, Fortnightly review: management of hypertension in pregnancy. BMJ 1999; 318: 1332-6.
[11] Lydakis C, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999; 12: 541-7.
[12] Pitzer M, et al. Child development after maternal tocolysis with beta-sympathomimetic drugs. Child Psychiatry Hum Dev 31: 165-82.
[13] Hadders-Algra, et al.

enrolled, an effort that would place tremendous burden on the healthcare system and does not seem justified based on the data available.

Because of the lack of data to support a signal for an effect of propranolol on later neurocognitive development and study design factors (poor retention, lack of a control group), I do not recommend that the sponsor be required to perform a post marketing study to evaluate the impact of use of propranolol in infants on neurological and cognitive development.

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/s/

MARY R SOUTHWORTH
02/10/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: January 27, 2014

To: Quynh Nguyen
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: (b) (4) **(propranolol) Oral Solution**
NDA: 205410
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on August 8, 2013, for (b) (4) (propranolol) Oral Solution ((b) (4) OPDP's comments are provided directly on the attached marked-up copy of the proposed PI. Our comments are based on the proposed labeling emailed to us on January 14, 2014.

OPDP has also reviewed the revised Carton and Container Labeling submitted by the sponsor on December, 20, 2013. We have no additional comments on the revised Carton and Container Labeling at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
01/27/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 27, 2014
To:	Norman Stockbridge, MD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	(b) (4) (propranolol hydrochloride)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 205-410
Applicant:	Pierre Fabre Pharmaceuticals, Inc.

1 INTRODUCTION

On May 17, 2013, Pierre Fabre Pharmaceuticals, Inc. submitted for the Agency's review a 505(b) (2) New Drug Application (NDA) 205-410 for (b) (4) (propranolol hydrochloride) oral solution. The proposed indication for (b) (4) (propranolol hydrochloride) oral solution is for the treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients 5 weeks to 5 months. The Reference Listed Drug (RLD) for this product is Inderal (propranolol hydrochloride), NDA 16-418.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCRP) on August 8, 2013, for DMPP and OPDP to review the Applicant's proposed patient labeling Patient Package Insert (PPI) and Instructions for Use (IFU)) for (b) (4) (propranolol hydrochloride) oral solution.

2 MATERIAL REVIEWED

- Draft (b) (4) (propranolol hydrochloride) oral solution PPI received on May 17, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 14, 2014.
- Draft (b) (4) (propranolol hydrochloride) oral solution IFU received on May 17, 2013, further revised on October 30, 2013 and received by DMPP and OPDP on October 30, 2013.
- Draft (b) (4) (propranolol hydrochloride) oral solution Prescribing Information (PI) received on May 17, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 14, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The appended IFU incorporates DMPP and DMEPA comments.

4 DISCUSSION

Pierre Fabre Pharmaceuticals, Inc. submitted a proposed Patient Package Insert as part of their NDA submission package for (b) (4) (propranolol hydrochloride) oral solution. DMPP, DCRP and DRISK met on December 5, 2013 and December 19, 2013 to discuss whether a Medication Guide is required for (b) (4) (propranolol hydrochloride) oral solution because of the risk of hypoglycemia. The intended patient population for which the drug product is proposed is particularly vulnerable to hypoglycemia because they cannot actively voice their symptoms, and because (b) (4) may mask the symptoms and signs of hypoglycemia. The group decided that Patient Labeling (Medication Guide) will be required under 21CFR208.1 (c) (1): "The drug product is one for which patient labeling could prevent serious adverse effects."

As part of this review, we converted the proposed PPI to a MG.

5 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
01/27/2014

ZARNA PATEL
01/27/2014

BARBARA A FULLER
01/27/2014

LASHAWN M GRIFFITHS
01/27/2014

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 Label and Labeling Memo

Date:	January 15, 2014
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	Lisa Khosla, PharmD, MHA Division of Medication Error Prevention and Analysis
Drug Name and Strength:	(b) (4) (Propranolol Hydrochloride) Solution, 4.28 mg/ml
Application Type/Number:	NDA 205410
Applicant/sponsor:	Pierre-Fabre Dermatologie
OSE RCM #:	2013-2863

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for (b) (4) (propranolol hydrochloride), NDA 205410, received on December 20, 2013 from the Applicant (Appendices A and B). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed labels and labeling under OSE Review # 2013-1353 dated November 27, 2013.

2 MATERIALS REVIEWED

DMEPA reviewed the labels and labeling received on December 20, 2013. We compared the revised labels and labeling against our recommendations in OSE Review # 2013-1353 dated November 27, 2013, to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised container labels and carton labeling determined the Applicant implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn at 301-796-2084.

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/s/

JACQUELINE E SHEPPARD
01/15/2014

LISA V KHOSLA
01/15/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 5, 2013

TO: Quynh M. Nguyen, Project Manager
Khin U, CDTL
Norman Stockbridge, Division Director

FROM: Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH**:** Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205410

APPLICANT: Pierre Fabre Dermatologie
45 Place Abel Gance
F-92100 Boulonge, France
Contact Person: John C. Kim, R.Ph., J.D. (U.S. Agent)
Pierre Fabre Pharmaceuticals, Inc.
8 Camput Drive, 2nd floor
Parsippany, NJ 07054
(973) 647-1640
Email: jkim@pfpharmausa.com

DRUG: (b) (4)® (propranolol) 3.75 mg/mL, oral solution
NME: No
THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: 1. Treatment of proliferating infantile hemangioma requiring systemic therapy to be initiated in patients aged five weeks to five months

CONSULTATION REQUEST DATE: June 17, 2013
INSPECTION SUMMARY GOAL DATE: December 17, 2013
DIVISION ACTION GOAL DATE: March 17, 2014
PDUFA DATE: March 17, 2014

I. BACKGROUND:

Pierre Fabre Pharmaceuticals, Inc. submitted an NDA for (b) (4) 3.75% oral solution requesting approval to support the use of (b) (4) for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy in infants aged five weeks to five months. The reference listed drug product basis for this submission is Inderal® (propranolol), NDA 16-418. Propranolol hydrochloride is a non-selective beta-adrenergic receptor blocking agent. (b) (4) was granted an orphan drug designation by the FDA on September 5, 2008. The proposed therapeutic dose of propranolol is 3 mg/kg/day to be administered in two separate doses of 1.5 mg/kg.

HIs are benign vascular tumors of childhood, characterized by endothelial cell proliferation. They are the most common soft-tissue tumors of childhood. All HIs exhibit a characteristic evolution with early rapid growth followed by a stabilization period and a slow spontaneous involution.

The sponsor proposes (b) (4) oral solution be indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged five weeks to five months of age. The proposed label states that (b) (4) be contraindicated in premature infants, for whom the corrected age of five weeks has not been reached, infants weighing less than two kilograms or four and a half pounds, (b) (4), know hypersensitivity to propranolol or excipients, asthma or history of bronchospasm, (b) (4), heart failure (b) (4). The most common adverse reactions (occurring in ≥ 10% of patients) reported in the proposed label were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting.

The sponsor submitted data from a randomized, controlled, multidose, multicenter, adaptive phase II/III study (Protocol V00400 SB 201) which they state provides sufficient evidence to support the indication of (b) (4) for the treatment of proliferating IH requiring systemic therapy in infants aged five weeks to five months. A brief description of the protocols is provided in the following section; further details may be found in the protocol and amendments.

Study Protocol V00400 SB 201: This is a randomized, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind). The study was a pivotal, multicenter, multi-dose, two-stage, adaptive design with treatment regimen selection at the end of the first stage. The following five treatment arms were investigated initially (Stage 1, prior to regimen selection following the interim analysis):

1. Regimen 1: 3 months V0400SB 1 mg/kg/day followed by 3 months placebo

2. Regimen 2: 6 months V0400SB 1 mg/kg/day
3. Regimen 3: 3 months V0400SB 3 mg/kg/day followed by 3 months placebo
4. Regimen 4: 6 months V0400SB 3 mg/kg/day
5. 6 months placebo

Subjects were to be treated for 24 weeks (6 months, from Day 0 to Week 24) and then followed up for a further 72 weeks (up to Week 96). The test product V0400SB oral solution (1.25, 2.50, and 3.75 mg/mL) was to be administered at 1 or 3 mg/kg/day, depending on the assigned regimen. Treatment was given twice a day (morning and late afternoon) and the required dose to be administered to the patient was to be calculated by the investigator at each visit and followed by the parent(s) until the next visit. A titration procedure was to be performed for the 3 mg/kg/day regimens, as follows:

1. Day 0: 1 mg/kg/day
2. Day 7: Increased to 2 mg/kg/day
3. Day 14: Increased to 3 mg/kg/day

A dummy titration was to be used for subjects assigned to 1 mg/kg/day in order to maintain double-blind conditions. In particular, all patients were to receive the same volume of product (0.4 mL/kg/dose), whatever the assigned treatment arm (doses were to be adjusted by the concentration of the administered products). Furthermore, even if none of the 3 mg/kg/day was to continue as Stage 2 recruits in order to limit information conveyed to observers at the interim analysis,V0400SB was to be administered for 3 or 6 months, depending on the assigned regimen. For the two 3-month regimens, placebo was to be administered for the last 3 months of treatment in order to maintain double-blind conditions. If one or both 3-month regimens were chosen at the end of Stage 1, Stage 2 patients assigned to the chosen regimens, were still to receive placebo for the last 3 months of V0400SB treatment arm in order to limit information conveyed to observers at the interim analysis. For the placebo, procedures (with dummy titration) were to be followed as described for the V0400SB treatment arm in order to maintain double-blind conditions. Stratified block randomization (two strata [age and IH localization] with two levels each) were to be applied in a 2:1 ratio (propranolol regimens:placebo). Full follow-up for long-term safety and efficacy analyses was to continue for a further 2 weeks (up to Week 96). Including the screening period, the maximum total study duration per subject was to be approximately 98 weeks.

Protocol V00400 SB 201 was conducted in 56 recruiting centers in 16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russia, Spain and the U.S.A). A majority of the subjects were from Western Europe (235 subjects, 51.5%, varying between 40.2% [41/102 subjects] in the 1 mg/kg/day 6 months arm and 63.6% [35/55 subjects] in the placebo arm), other European countries (73 patients, 16%) or U.S.A.-Canada (71 subjects, 15.6%). Forty (8.8%) subjects were from other American countries and 37 (8.1%) form Oceania. The most frequent countries of origin of the patients were, in descending order, France (114 subjects, 25.0%; French subjects were slightly more frequent in the placebo arm: 38.2% than in the other arms: between 17.6% and 27.7%), Germany (60 subjects, 13.2%), Spain (59 subjects, 12.9%), and the U.S.A. (53 subjects, 11.6%). Six other countries recruited more than 10 subjects each

(Peru: 35 subjects, 7.7%; Australia: 32 subjects, 7.0%; Poland: 26 subjects, 5.7%; Canada: 18 subjects, 3.9%, Lithuania: 18 subjects, 3.9%; and Hungary: 11 subjects, 2.4%).

Objectives
The primary objective of the study was to identify the appropriate dose and duration of propranolol treatment and to demonstrate its superiority over placebo based on the complete/nearly complete resolution of target IH at Week 24.

The safety objective was to document the safety profile of the four regimens of propranolol in the treatment of IH in infants aged one to five months (35 to 150 days) at inclusion.

Endpoints
The primary endpoint was a complete or nearly complete resolution of target IH at Week 24 (W24) assessed centrally. The evolution of target IH from baseline to W24 was evaluated based on the intra-patients blinded centralized independent qualitative assessment of W24 photographs of the target IH compared to baseline. The digital photographs of each target hemangioma in the (b) (4) study was to be acquired by the site investigators. The investigators were to be fully trained and evaluated in the standardized acquisition procedures prior to their first patient photograph acquisition. The acquisition procedures were to ensure consistency in patient positioning, lighting, exposure and distance from the camera, allowing homogenization of the acquisition across visits. Safety was to be assessed by adverse event monitoring, laboratory assessments, and physical evaluations.

Eligibility Criteria
Male and female patients who were 35 to 150 days old with a facial proliferating IH (target hemangioma) with the largest diameter of at least 1.5 cm, requiring systemic therapy were to be entered in the trial. The details of inclusion and exclusion criteria for this study are found in the study protocol.

Study Visits and Procedures
After eligibility checking and informed consent signature by the parent(s) or legal guardian, subjects were randomized in a 2:2:2:2:1 ratio to receive respectively: one of four regimens of propranolol (Regimen 1: 1 mg/kg/day for 3 months; Regimen 2: 1 mg/kg/day for 6 months, Regimen 3: 3 mg/kg/day for 3 months; Regimen 4: 3 mg/kg/day for 6 moths) or placebo.

A subject's complete participation up to W24 comprised 11 scheduled visits:

- A screening visit (when possible, the screening visit could be done on the same day as the baseline visit),
- 10 visits during the 24-week study treatment period, starting on baseline visit (Day [D] 0, 0 to 14 days after the screening visit, then D7, D14, D21, W5, W12, W16, W20, and W24 (end of study treatment: EOT).

In the case of a worsening IH during the study treatment period for which the Investigator considered it was necessary for the subjects' well-being to administer a new treatment of his/her choice, the study treatment was permanently discontinued.

Protocol Amendments

II. RESULTS (by Site):

Name of CI	Protocol # , Site #, and # of Subjects	Inspection Date	Final Classification
Sheila Friedlander, M.D. Rady Children's Hospital San Diego Pediatric & Adolescent Dermatology San Diego, CA	Protocol #V00400 SB 201 Site #7105 16 subjects	9/10/13-9/17/13	NAI
Juliette Mazereeuw, M.D. Hopital des Enfants Departmbet Cardio-Pediatrique 330 avenue de grande Bretagne 31100 Toulouse, France	Protocol #V00400 SB 201 Site 0508 28 subjects	6/24/13-6/28/13	NA
Instituto Nacional de Salud del nino Avenida de Brasil 600 Brena, Lima Peru	Protocol # V00400 SB 201 Site 5002 17 subjects	8/20/13-8/23/13	NA
Institut de Recherche Peirre Fabre (IRPF) 3 Avenue Hubert Curien 31000 Toulouse France	Protocol # V00400 SB 201	7/29/13-8/2/13	NA

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.
NA = Conducted by EMA; OSI classifications not applicable.

Choice of Sites

In discussions with the review division and the EMA, we noted that both OSI and EMA had selected sites in France (identical site) and Peru (two separate sites). Since the EMA had already scheduled inspections in France and Peru, as well as of the sponsor IRPF, OSI decided to obtain the results of the EMA inspections prior to reproducing similar or identical inspections. If serious findings impacting on study data integrity or subject safety were identified by the EMA, OSI would have issued inspections to be conducted by ORA. Since no findings were identified in this category, the inspections summarized below in France (clinical investigator and sponsor) and Peru were conducted by the EMA.

1. Sheila Friedlander, M.D.
   Rady Children's Hospital
   San Diego Pediatric & Adolescent Dermatology
   San Diego, CA 92123

   a. **What was inspected**: The inspection was conducted as a data audit for NDA #205410. At this site, 19 subjects were screened, 16 subjects were randomized, and 13 subjects completed the study. Three subjects were discontinued due to lack of efficacy. Included in the inspection were review of individual responsibility, adverse events, randomization, blinding procedures, photographs of lesions, informed consent documents (100%), monitoring, drug accountability, and primary efficacy outcome data. E-CRFs were spot checked with source records for Subjects 710503, 710504, 710505, and 710506.

   b. **General observations/commentary**: One subject's Spanish speaking parent received and signed an informed consent document in English presented by a translator prior to IRB approval of the Spanish language form. The blind for Subject 710501 was broken at Dr. Friedlander's request when the subject was not improving; the subject was in the placebo arm. No other significant regulatory violations were noted, and a Form FDA 483 was not issued. There was no evidence noted of bias against study drug by site personnel.

   c. **Assessment of data integrity**: The data generated at Dr. Friedlander's site in support of clinical efficacy and safety may be considered acceptable and may be used in support of the pending application.

The remaining two clinical investigator inspections in France and Peru as well as the sponsor inspection of IRPF in France were conducted by the EMA and the results communicated to OSI. The major structure of EMA inspections consists of classification of regulatory deficiencies as Critical (CR), Major MA), and Minor. Given below are definitions and potential consequences of these classifications:

- Critical: Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of the data. Possible consequences include rejection of data and/or legal action required.
- Major: Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Possible consequences include data being rejected and/or legal action required.
- Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of the data. Possible consequences include the need for

improvement of conditions, practices and processes.

2. Pr Juliette Mazereuw-Hautier
Hopital Larrey – service de Dermatologie
24, Chemin de Pouvourville
TSA 30030
31059 Toulouse Cedex 9

a. What was inspected: The inspection was conducted as a data audit for EMA Inspection reference INS/GCP/2013/016; the results were shared with OSI. At this site, 29 subjects were screened, and 28 subjects were enrolled between March, 2010 and June, 2013. There were 13 subjects who were prematurely withdrawn, 12 of who continued in the follow-up portion of the trial and one who was lost to follow-up. Included in the inspection were investigator CVs, eCRF completion guidelines, patient diaries and instruction cards, study site personnel names and signatures, list of subjects, site visit log, monitor initiation visit, investigational product handling, IVRS manual, verification of adverse events, including SAEs, and study related correspondence. Also verified were source data in hospital files and in principal investigator files.

b. General observations/commentary: 100% of source data were available in hospital files and investigator patient files and verified, appropriate investigational drug management was noted, all informed consent documents were confirmed, and inclusion/exclusion criteria verified. At this site the EMA inspectors noted 2 critical, 16 major, and 15 minor violations. A listing of these violations was submitted to the sponsor who responds in writing. The violations and responses will be included below only when the Medical Officer judges them to be potentially relevant to study efficacy outcome or subject safety. Summarized below will be significant observations only:

Critical

1. The data reported in the eCRF were not validated by the investigator; the study eCRF design does not allow any partial validation until the end of the study, which was still in progress during the inspection.
2. Two patients with low neutrophil counts (400 and 700 cells/mm^3) that were not labeled "Not Clinically Significant" (NCS) by the investigator who did not give a justification, nor did the sponsor challenge this classification. The site subsequently changed the classification of the subject with 400 cells/mm^3 to Clinically Significant (CS); recheck showed that the neutrophil count had increased to 2362/mm^3. The sponsor was also queried about this issue, and it will be further addressed in the sponsor inspection section.

Major

1. ECGs were accessible to a member of the investigator team (MA4), with the possibility of unblinding as a result.

2. Several IH diameters were under the minimum size specified in the protocol inclusion criterion; the IH diameter measures at inclusion were frequently missing in the patient files. The investigator at this site included induration in the measurement, as did 47 other sites by sponsor polling. Six sites included only lesion size. Of note, there was no requirement to record the actual lesion size in the centralized assessment, it only had to be noted that it met the minimum requirement of 1.5 cm.
3. The medical file of one subject (050803) was lost and the ECGs from one visit of two additional subjects (050822, 050823) were missing. (MA7). After inquiry to the sponsor, it was noted that only the nurse chart for Day 0, Day 7, and Day 14 and ECG tracings for Day 0 and Day 11 were missing for Subject 050803.
4. About 40% of the pre-dose pin-prick glycaemia tests were performed more than an hour before treatment administration, which would not allow the PI to detect a hypoglycemic state at the time of study drug intake. Although this is a protocol violation, there were no episodes of hypoglycemia during the study.

There were 34 monitoring visits during the study conducted between November, 2009 and February, 2013, both by the CRO and the sponsor.

c. Assessment of data integrity: The inspection did not question the patient's existence, their participation in the trial and the conduct of the study visits as required by the protocol. All patients had a proliferating IH, were of the expected age at inclusion and their parents have all signed an informed consent form before any study-related procedure. Two issues which have potential study wide implication (low neutrophils not classified as CS or AEs and size of initial lesions) will be discussed further in the sponsor inspection Section 4. Despite the GCP violations noted at this site, the data may be considered adequate and may be used in support of the pending application.

3. Dr. Hector Caceres
Instituto Nacional de Salud del nino
Avenida Brasil 600,
Brena, Lima
Peru

a. What was inspected: The inspection was conducted as a data audit for EMA Inspection reference INS/GCP/2013/016; the results were shared with OSI. At this site, 17 subjects were screened, and 17 subjects were randomized between August, 2011 and April, 2012. There was one subject who was prematurely withdrawn due to a non-serious SAE. Included in the inspection were investigator CVs, eCRF completion guidelines, patient diaries and instruction cards, study site personnel names and signatures, list of subjects, site visit log, monitor initiation visit, investigational product handling, IVRS manual, verification of adverse events,

including SAEs, and study related correspondence. Also verified were source data in hospital files and in principal investigator files.

b. General observations/commentary: 100% of source data were available in hospital files and investigator patient files and verified, appropriate investigational drug management was noted, all informed consent documents were confirmed, and inclusion/exclusion criteria verified. At this site the EMA inspectors noted 1 critical, 7 major, and 1 minor violation. Descriptions of these violations were submitted to the sponsor who provides a written response; these violations and responses will be included below when the Medical Officer considers them potentially relevant to study efficacy outcome or subject safety.

Critical

It appeared that patient diaries were not always completed by caregivers or patients/relatives of the subjects, but sometimes by a common third person.

Major

1. Changes to the initial assessment of the objective hemangioma were made after the physical presence of a medical department representative of the sponsor, who was not a monitor or auditor. The assessments were made based on the photographs. In the investigator's response, the investigator stated that all changes were made with the investigator's agreement. The sponsor also notes that the described assessments of the photographs were performed in a blinded manner.
2. There was no evidence of the full validation of the system used for exporting data from the eCRF system to the audit trial viewer presented to the inspector in order to check the audit trial. The sponsor later presented evidence of the validity of the system.
3. There was no monitoring of temperature extremes of the drug product during shipments (especially the low temperatures during the airborne shipment). The sponsor states that the storage temperature requirements for the investigational product were "below +30^{o}C – do not freeze", such that product stability should not be impacted.

c. **Assessment of data integrity**: The inspection did not question the patient's existence, their participation to the trial and the conduct of the study visits as required by the protocol. All patients had a proliferating IH, were of the expected age at inclusion, and their patents have all signed an informed consent form before any study-related procedure. Despite the GCP violations noted at this site, the data may be considered adequate and may be used in support of the pending application.

4. Pierre Fabre Dermatologie
Institut de echerche Pierre Fabre (IRPF)
3 avenue Hubert Curien

3100 Toulouse
France

a. What was inspected: The inspection was conducted as a data audit for EMA Inspection reference INS/GCP/2013/016; the results were shared with OSI. A total of 460 subjects were enrolled at 56 sites. Included in this inspection were monitoring processes, review/supervision of protocol deviations, handling of trial data, randomization process, collection of AEs and SAEs, compliance with protocol and statistical analysis, relevant aspects of the trial master file, and the sponsor/CRO audit and quality assurance system.

b. General observations/commentary: Overall, the study was well-conducted. There was 1 critical, 13 major, and 5 minor findings reported. The most significant will be summarized below.

Critical

Regarding neutrophil counts, the inspectors noted that six subjects presented with a neutropenia classified as Grade 4. All of these subjects were randomized to the propranolol arm: five presented with neutropenia during the propranolol treatment phase and one during the placebo treatment phase. Only two of these were reported as AEs in the CSR. On reevaluation one additional case was considered to be an AE; the remainder of the investigators maintained their initial assessment of NCS.

Major

1. The data could be entered in the eCRF without any password and the data submitted in the CSR were not formally validated by the investigators. At Week 24 when this was discovered, individual access codes were set up. Additionally, data certification of all data entered for each patient into the eCRF up to Week 24/EOT were obtained from all principal investigators. (This finding was downgraded from critical).
2. An underutilization of subject diaries was noted during inspection of clinical investigator sites. When the sponsor explored this issue by polling the sites, it was found that out of 445 documented Week 96 or EOS visits:
    - 19.3% of diaries were lost
    - 5.2% of returned diaries had not been used by the parents.

   The sponsor notes that the diaries were intended to facilitate discussion of study related events, rather than to serve as the sole source of AE reporting. After examination of diaries collected at the end of the study, no treatment emergent SAEs were identified.
3. The primary analysis database was unlocked twice, the second time after the randomization code release and after performing statistical analysis. This was felt by the inspectors to reflect insufficient quality control. The sponsor notes that although some tables were altered based on analysis of discrepancies, there was no impact on the primary efficacy analysis.
4. The failure of the protocol to provide specific objective instructions as to

how IH measurements was again noted. When polled, 48 sites used induration plus lesion size, while 6 used only lesion size.

Other less significant findings included data entry errors, protocol violations, use of incorrect protocol or informed consent document version.

c. **Assessment of data integrity**: One of the most significant issues identified was not a GCP violation, but rather a failure to precisely identify in the protocol how the IH lesions should be measured. Since the majority of sites (48/54) used lesion size + induration, an overall effect on the study seems unlikely. Failure to classify some cases of Grade 4 neutropenia as "Clinically Significant" may have resulted in missing AEs/SAEs; when this issue was examined by the sponsor, the number appears to be relatively small (approximately three subjects). Despite minor GCP violations noted, the data may be considered adequate and may be used in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This clinical inspection summary contains the results of an ORA/OSI conducted domestic inspection as well as the results of two EMA conducted foreign inspections in France and Peru and an inspection conducted in France of the sponsor IRPF. The inspection of Dr. Friedlander's site was unremarkable. One of the most significant issues identified at the foreign sites and the sponsor was not a GCP violation, but rather a failure to precisely identify in the protocol how the IH lesions should be measured. Since the majority if sites (48/54) used lesion size + induration, an overall effect on the study seems unlikely, but the review division may wish to compare the two sets of sites, since the six sites using size alone might underestimate lesion size at enrollment compared to the remainder of sites. Failure to classify some cases of Grade 4 neutropenia as "Clinically Significant" may have resulted in missing AEs/SAEs; when this issue was examined by the sponsor, the number appears to be relatively small (approximately three subjects). Failure to collect subject diaries has the potential to underestimate AEs, but the diaries were intended to be used at subject visits as a tool. Despite minor GCP violations noted, the data may be considered adequate and may be used in support of the pending application.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
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Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN D THOMPSON
12/09/2013

KASSA AYALEW
12/09/2013

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

Label, Labeling and Packaging Review

Date:	November 27, 2013
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	(b) (4) (Propranolol) Oral Solution 3.75 mg/ml
Application Type/Number:	NDA 205410
Applicant/sponsor:	Pierre Fabre Dermatologie
OSE RCM #:	2013-1353

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for [redacted] for areas of vulnerability that can lead to medication errors.

1.1 PRODUCT INFORMATION

The labeling submissions dated August 1, 2013 and September 13, 2013 provide the following product information:

- Active Ingredient: Propranolol
- Indication of Use: Treatment of proliferating infantile hemangioma requiring systemic therapy
- Route of Administration: Oral
- Dosage Form: Oral Solution
- Strength: 3.75 mg/ml
- Dose and Frequency: 3 mg/kg/day in divided doses twice daily for up to 6 months. See schedule below for titration:

  Dose Titration and Adjustment

  Week 1 (Starting)

  [redacted] as divided doses of [redacted] mg/kg twice daily

  Week 2

  [redacted] as divided doses of [redacted] twice daily

  Week 3 (Maintenance)

  [redacted] as divided doses of [redacted] twice daily up to 6 months
- How Supplied: 120 ml amber glass bottle with a [redacted] cap and a 5 ml syringe
- Storage: 77° F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C). After first opening, the product can be stored for 2 months.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for propranolol solution medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the [redacted] labels, labeling, and container with syringe submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS databases using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	September 6, 2013, no time limits
Drug Name	Verbatim Product Name: Propranolol% OR Inderal% (we reviewed the results, and manually selected oral propranolol solution terms).
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 25 cases. We reviewed each case for relevancy and duplication. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when the reporter provided sufficient information.[1] After individual review, 23 cases were not included in the final analysis for the following reasons:

- Intentional overdose (n = 10)
- Multiple drug overdose (n = 10)
- Product quality issue unrelated to medication error (n =1)
- Wrong drug dispensed (n =2)

2.2 LABELS, LABELING, AND PACKAGING

Using the principles of human factor and Failure Mode and Effects Analysis,[2] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted 09/13/2013 (Appendix B)
- Carton Labeling submitted 09/13/2013 (Appendix C)
- Insert Labeling submitted 08/01/2013 (no image)
- Diagram of oral syringe submitted 05/17/2013 (Appendix D)
- Physical samples of bottle with oral dosing syringe (no image)

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[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed September 6, 2013.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b) (4) product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two propranolol medication error cases remained for our detailed analysis. These two cases took place between March 2005 and April 2007.

Wrong Strength Dispensed

One case involved an infant who was prescribed a 1 mg/ml concentration of propranolol hydrochloride by a cardiologist, but was dispensed 4 mg/ml solution by a pharmacist. This prescription was subsequently refilled with the incorrect strength. The reported outcome was hospitalization of the infant. No contributing factors were reported.

Wrong Dose Dispensed

One case involved a neonate who was dispensed 1.5 ml three times daily instead of 0.5 ml three times daily of propranolol solution. The error was caught during discharge counseling from the hospital and the child did not receive the medication. No contributing factors were reported.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

During our review of this product, we observed that unlike propranolol hydrochloride solutions currently on the market, the Applicant has chosen to use the name of the active moiety, propranolol, instead of the name of the salt, propranolol hydrochloride. Accordingly, the Applicant has based the strength of this product on the active moiety, 3.75 mg/mL, instead of the salt. This appears consistent with the USP salt nomenclature rule. However, the introduction of this discrepancy to the market may be a source of confusion. Although this product is seeking approval only for the treatment of proliferating infantile hemangioma, in the event that providers use this product interchangeably with other propranolol hydrochloride solutions, overdoses or underdoses may occur. We raised our concerns regarding the salt nomenclature during a team meeting held on September 19, 2013. We recommended ONDQA consider the risk for medication errors in their decision regarding salt nomenclature. ONDQA agreed there was a safety concern, and decided to retain the name of the salt as an exception to the USP nomenclature rule. This decision was conveyed to the Applicant by ONDQA already.

Our evaluation of the labels and labeling determined the dosage and administration section of the package insert labeling could be improved for clarity. We also identified inconsistency in the expiration dating between the bottle label and the package insert labeling. In a response to information request received September 13, 2013, the Applicant clarified that the correct expiration date is 2 months after bottle opening. This

date should be incorporated consistently throughout all the labels and labeling for this product.

The Applicant has included the statement "Alcohol/Sugar free" on the proposed container label and carton labeling. Per the Chemistry, Manufacturing and Controls (CMC) reviewer, this statement is an accurate reflection of the formulation and can remain on the label and labeling. The Office of Prescription Drug Promotion (OPDP) has determined that the statement is acceptable as long as long as this information is reflected in the prescribing information also. We recommend moving this statement to the side panel of the container label so it does not compete with important information on the principal display panel (PDP).

The Applicant provided a sample of the oral dosing device for review. The dosing syringe is clearly marked for oral use and the graduations cover the entire dosing range. The graduation markings are on the right side with the exception of the first marking for the 0.3 ml dose, which is on the left side of the side of the syringe. This differs from most oral dosing syringes available over-the-counter; however, we do not believe this is likely to cause confusion that can lead to medication error, and we recognize it may not be feasible to make design changes to the syringe at this point in the application. In response to an information request concerning the procurement of additional syringes and syringe adaptors, the Applicant indicated that the proposed distribution model for (b) (4) is through a specialty pharmacy that will only dispense entire bottles. In addition, replacement syringes will be available and could be shipped to the caregiver overnight if needed. The agency will monitor for any postmarketing reports of confusion related to the oral dosing device.

If approved, (b) (4) will introduce a new strength to the market. DMEPA acknowledges that the introduction of a new strength and concentration of propranolol hydrochloride increases the risk for dosing errors. However, DMEPA recognizes that other oral solution products are available in multiple concentrations. Therefore, the additional risk of medication error will need to be mitigated through labeling strategies that bring prominence to the strength of (b) (4)

4 CONCLUSIONS

DMEPA concludes the proposed label and labeling can be improved to promote the safe use of the product and to mitigate the risk for confusion with the other commercially available propranolol solutions.

5 RECOMMENDATIONS

DMEPA recommends the Applicant implement the following recommendations prior to approval of this NDA:

5.1 COMMENTS TO THE DIVISION

A. Full Prescribing Information, Section 2

1. The product expiration date is inconsistent between various sections of the prescribing information. All sections should reflect the appropriate expiration date of two months after bottle opening consistently.
2. If [redacted] (b) (4) is not interchangeable with other propranolol products, we recommend including a statement reflecting this information.
3. Clarify the amount of liquid the medication can be diluted in before being given to the patient.

5.2 COMMENTS TO THE APPLICANT

A. Bottle Container Label

1. Remove or minimize and relocate the Pierre Fabre logo at the top of the principal display panel so it does not compete with the proprietary name, established name, and strength.
2. Revise the presentation of the proprietary name from all caps (i.e. [redacted] (b) (4) to title case (i.e. [redacted] (b) (4) to improve readability of the name.
3. Move the statement of strength immediately below the established name and increase its prominence by increasing the font size and ensuring adequate contrast with the white background.
4. Decrease the font size of the net quantity statement, "120 mL Bottle" to decrease its prominence.
5. Bold the Discard unused portion…opening" statement on the side panel and move this statement to the top of the side panel for increased prominence.
6. Debold the "Rx only" statement and decrease its font size.
7. Move the "Alcohol/Sugar Free" statement to the side panel. Additionally, debold this statement.
8. Add an area on the side panel for the end user to write the date opened. In order to accommodate this, consider condensing the manufacturer statement.

B. Carton Labeling

1. See comments A1 to A7 above.
2. We recommend replacing the computer generated graphic of the bottle and oral dosing syringe with an actual picture (photo) of the final bottle and oral syringe.
3. Ensure the lot number and expiration date are included.

If you have further questions or need clarifications, please contact Quynh Nguyen, project manager, at 301-796-0510.

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE E SHEPPARD
11/27/2013

IRENE Z CHAN
11/27/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205-410 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: propanolol HCl Dosage Form: Oral solution Strengths: 3.75 mg/mL		
Applicant: Pierre Fabre Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 5-17-13 Date of Receipt: 5-17-13 Date clock started after UN:		
PDUFA Goal Date: 3-17-14	Action Goal Date (if different):	
Filing Date: 7-16-13	Date of Filing Meeting: 6-27-13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment of proliferating infantile hemangioma (IH) requiring systemic therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 104,390	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Orphan exception; PD3013308

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		Applicant requested 7-year Orphan Exclusivity.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X			

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*		X		Orphan designation

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 4-24-12 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** Division response letters dated 1-2-11; 4-5-10; 1-7-10; 10-2-09; Meeting minutes dated 11-16-09 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 27, 2013

BLA/NDA/Supp #: 205-410

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Propanolol HCl

DOSAGE FORM/STRENGTH: Oral Solution

APPLICANT: Pierre Fabre Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of proliferating infantile hemangioma (IH)

BACKGROUND: Pierre Fabre Pharmaceuticals, Inc. submitted this 505(b)(2) NDA for (b) (4) (propranolol) Oral Solution, 3.75 mg/mL. The proposed indication is for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy, to be initiated in infants aged 5 weeks to 5 months. The proposed dose is 3 mg/kg/day to be administered as 2 separate doses of 1.5 mg/kg, using a dedicated oral dosage syringe. The reference listed drug (RLD) that is the basis for this NDA submission is Inderal (propranolol HCl), NDA 16-418. (b) (4) was granted an orphan designation for the proposed indication on September 5, 2008 (Orphan Designation #08-2667).

This NDA includes an assessment of published non-clinical studies and refers to the RLD, Inderal, to fulfill the requirements for non-clinical studies.

In support of approval, the clinical development is based on three clinical studies:

- Two pharmacokinetic studies (Study V00400 SB 101 2A in healthy adults and Study V00400 SB 102 in infants with IH)
- One pivotal Phase II/III study (Study V00400 SB 201)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Khin U		Y
Clinical	Reviewer:	Khin U	Y

	TL:	Thomas Marciniak	N
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Divya Menon-Andersen	Y
	TL:	Rajnikanth Madabushi	Y
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Baichun Yang	Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Prafull Shiromani Kareen Riviere (Biopharm)	Y Y
	TL:	Kasturi Srinivasachar Angelica Dorantes (Biopharm TL)	Y N
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kim Defronzo	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Rao Kambhampati (ONDQA)		
Other attendees	Norman Stockbridge, Steve Grant, (DCRP); Colleen Locicero (ODE1); Jie Li, Cherye Milburn (OSE); Meghan Delmastro-Greenwood, Kelly Quesnelle		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO BA/BE studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES ☐ NO

If no, explain:	
• Advisory Committee Meeting needed? **Comments**: No AC meeting needed. ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 10-31-13

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUYNH M NGUYEN
08/09/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 205-410

Application Type: New NDA

Name of Drug: (b) (4) (propranolol) Oral Solution, 3.75 mg/mL

Applicant: Pierre Fabre Pharmaceuticals, Inc.

Submission Date: May 17, 2013

Receipt Date: May 17, 2013

1.0 Regulatory History and Applicant's Main Proposals

Pierre Fabre Pharmaceuticals, Inc. submitted this 505(b)(2) NDA for the proposed indication of treatment of proliferating infantile hemangioma (IH) requiring systemic therapy, to be initiated in infants aged 5 weeks to 5 months. The proposed dose is 3 mg/kg/day to be administered as 2 separate doses of 1.5 mg/kg, using a dedicated oral dosage syringe. The reference listed drug (RLD) that is the basis for this NDA submission is Inderal (propranolol HCl), NDA 16-418. (b) (4) was granted an orphan designation for the proposed indication on September 5, 2008 (Orphan Designation #08-2667).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 7, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Please correct to 1/2 inch margins on all sides.*

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Please correct.*

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Please correct the headings to be in the center of the horizontal line.*

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Please add reference for the first bulletted statement under DOSAGE AND ADMINISTRATION.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Please place the "Initial U.S. Approval:" followed by the 4-digit year immediately beneath the product title.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

NO 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment: *Please correct so that the contraindications in the HL and FPI are listed in the same order. Also, the bullet "*

NO (b) (4)

is listed in the HL Contraindications but is not listed in the FPI Contraindications. This contraindication must also appear in the FPI if it appears in HL.

24. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *Please correct.*

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

NO 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: *Please correct the text to the above statement and remove the line following the statemetn in your proposed labeling.*

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

NO 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment: *Please embolden the heading.*

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *Add a space between the words "subsections" and "omitted" in the statement: "*Sections or subsections omitted from the Full Prescribing Information are not listed." Un-bold the statement and add a period to the end of the statement. Delete the horizontal line that immediately precedes the statement.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *In subsection 6.1 Clinical Trials Experience, correct the lowercase letter "p" to uppercase letter "P" in the cross-reference "[see Warnings and precautions (5.x)]."*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

Comment: *Please correct text to as in the statement above.*

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Please correct text to (without quotation marks): "See FDA-approved patient labeling (Patient Information and Instructions for Use)".*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUYNH M NGUYEN
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attachment	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
LEFRANCOIS Pascal	President
FIRM/ORGANIZATION	
PIERRE FABRE DERMATOLOGIE	
SIGNATURE	**DATE** *(mm/dd/yyyy)*
	13 Aug 2013

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

FORM FDA 3454 (10/09)

PSC Graphics (301) 443-1090 EF

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