

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205410Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205410	
		NAME OF APPLICANT/NDA HOLDER Pierre Fabre Dermatologie	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) HEMANGIOL			
ACTIVE INGREDIENT(S) Propranolol Hydrochloride		STRENGTH(S) 3.75 mg/mL (expressed in propranolol base)	
DOSAGE FORM Oral solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,338,489		b. Issue Date of Patent 12/25/2012	c. Expiration Date of Patent 10/16/2028
d. Name of Patent Owner Universite Victor Segalen--Bordeaux 2		Address (of Patent Owner) 146 RUE LEO SAINAT	
		City/State BORDEAUX	
		ZIP Code 33076 FRANCE	FAX Number (if available)
		Telephone Number 0031 (0)557 571 010	E-Mail Address (if available) Jl.Chagnaud@ast-innovations.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) HARNESS, DICKEY and PIERCE		Address (of agent or representative named in 1.e.) PO BOX 228	
		City/State BLOOMFIELD HILLS / MI 48303	
		ZIP Code MI 48303	FAX Number (if available) (248) 641-0270
		Telephone Number (248) 641-1600	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1, 2, 4, 5, 12-14, 16, and 17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) The cited claims read on administration of an oral solution of propranolol at a dosage of less than or equal to 5 mg/kg/day to treat proliferating infantile hemangioma, as indicated.
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5. No Relevant Patents

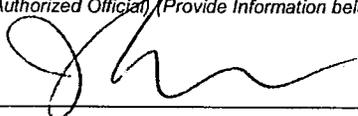
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

03/08/2013

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John C. Kim, RPh, JD

Address

Pierre Fabre Pharmaceuticals Inc
8 Campus Drive, 2nd Floor

City/State

Parsippany, NJ

ZIP Code

07054

Telephone Number

1 (973) 647-1640

FAX Number (if available)

1 (862) 207-7077

E-Mail Address (if available)

jkim@pfpharmausa.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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.

Patent Certification

The reference listed drug for which this 505(b)(2) application relies upon is INDERAL (propranolol hydrochloride) 80 mg Tablets, NDA # 016418. The NDA holder for NDA 016418 is Akrimax Pharms.

Based on the patent and exclusivity information provided in the *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (updated 24 July 2013), the undersigned states that there are no unexpired patents or unexpired exclusivity for INDERAL (propranolol hydrochloride) 80 mg tablets.



John C. Kim, RPh, JD
Vice President of Quality Assurance,
Regulatory Affairs and Vigilance
US Agent for PIERRE FABRE DERMATOLOGIE

30 July 2013

Date

EXCLUSIVITY SUMMARY

NDA # 205-410

SUPPL #

HFD #

Trade Name Hemangeol Oral Solution, 4.28 mg/mL

Generic Name propranolol hydrochloride

Applicant Name Pierre Fabre Pharmaceuticals, Inc.

Approval Date, If Known 3-14-14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years (orphan exclusivity)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 16-418

Inderal (propranolol hydrochloride) Tablets

NDA#

NDA#

Note: Multiple extended release capsules, injectables, and immediate release tablets. Refer to the Orange Book for complete list.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study V00400 SB 101 2A
Study V00400 SB 102
Study V00400 SB 201

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study V00400 SB 101 2A
Study V00400 SB 102
Study V00400 SB 201

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 104,390

!
!
YES ! NO
! Explain:

Investigation #2

IND # 104,390

!
!
YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Quynh Nguyen, PharmD, RAC
Title: Regulatory Project Manager, Division of Cardiovascular and Renal Products
Date: 3-14-14

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

NORMAN L STOCKBRIDGE
03/14/2014

Pediatric Page

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.

NDA 205-410

(b) (4) (propranolol)
1.3.3 Debarment Certification

1.3.3 Debarment Certification

The undersigned hereby certifies that PIERRE FABRE DERMATOLOGIE 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 the (b) (4) (propranolol) NDA 205-410.



John C. Kim, RPh, JD
Vice President of Quality Assurance,
Regulatory Affairs and Vigilance
US Agent for PIERRE FABRE DERMATOLOGIE

Date :

17 May 2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205-410 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Hемangeol Established/Proper Name: propranolol hydrochloride Dosage Form: Oral Solution, 4.28 mg/mL		Applicant: Pierre Fabre Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Quynh Nguyen, PharmD, RAC		Division: Cardiovascular and Renal Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 3-14-14</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>3-17-14</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 5
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old anti
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 3-14-14
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	3-7-14; 10-11-12 2-14-14; 8-7-13; 10-5-12
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 3-14-14; 8-9-13; 8-8-13 DMEPA: <input type="checkbox"/> None 3-10-14; 2-26-14; 2-21-14; 1-15-14; 8-7-13 DMPP/PLT (DRISK): <input type="checkbox"/> None 1-27-14 OPDP: <input type="checkbox"/> None 1-27-14 SEALD: <input type="checkbox"/> None 3-11-14 CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	8-9-13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 2-27-14
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Exempt from PREA because of orphan indication.</u> 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4-24-12
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-5-14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-7-14; 2-7-14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	12-20-13; 6-27-13; 5-31-13
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	12-20-13 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 1-21-14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 12-9-13
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-13-14; 6-30-13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-18-14; 7-8-13
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-7-13; 5-28-13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 3-7-14; 1-7-14; 12-31-13; 7-5-13; 6-24-13
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 12-5-13; 6-3-13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		12-31-13 CMC Review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 3-7-14 (see 3-7-14 CMC Memo-to-File for EER printout) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

QUYNH M NGUYEN
03/19/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205410

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pierre Fabre Dermatologie
c/o Pierre Fabre Pharmaceuticals, Inc.
8 Campus Drive, 2nd floor
Parsippany, NJ 07054

ATTENTION: John C. Kim
Vice President Regulatory Affairs, Quality Assurance & Vigilance

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) dated and received May 17, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride Oral Solution, 4.28 mg/mL.

We also refer to your correspondence, dated and received February 5, 2014, requesting review of your proposed proprietary name, Hemangeol. We have completed our review of the proposed proprietary name, Hemangeol, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Quynh Nguyen, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/07/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205410

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Pierre Fabre Dermatologie
c/o Pierre Fabre Pharmaceuticals, Inc.
8 Campus Drive, 2nd floor
Parsippany, NJ 07054

ATTENTION: John C. Kim
Vice President Regulatory Affairs, Quality Assurance & Vigilance

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) dated and received May 17, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Propranolol Oral Solution, 3.75mg/mL.

We also refer to:

- Your correspondence, dated and received May 22, 2013, requesting review of your proposed proprietary name, (b) (4)
- Your correspondence, dated and received January 14, 2014, requesting reevaluation of the proposed proprietary name, (b) (4)
- Our teleconference held on February 3, 2014, to discuss the proposed proprietary name, (b) (4)

We acknowledge receipt of your correspondence, dated and received February 5, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of February 5, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Quynh Nguyen at 301-796-0510.

Sincerely,

{See appended electronic signature page}

Cherye Milburn
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CHERYE D MILBURN
02/25/2014



NDA 205410

LABELING PMR/PMC DISCUSSION COMMENTS

Pierre Fabre Pharmaceuticals, Inc.
Attention: Mr. John C. Kim
8 Campus Drive, 2nd floor
Parsippany, NJ 07054

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) dated May 17, 2013, received May 17, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (propranolol HCl) Oral Solution, 4.28 mg/mL.

We also refer to our July 17, 2013 letter in which we notified you of our target date of February 17, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On October 30, 2013, we received your October 29, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

If you have any questions, please call me at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:

Revised labeling for Content of Labeling

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

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/s/

QUYNH M NGUYEN
02/13/2014

MEMORANDUM OF TELECONFERENCE

MEETING DATE: February 3, 2013

TIME: 11:00 am

LOCATION: WO Bldg 22, Room 4396

DRUG NAME: (b)(4) (propranolol hydrochloride) NDA 205410

TYPE OF MEETING: Teleconference with Pierre Fabre Pharmaceuticals.

MEETING RECORDER: Cherye Milburn, SRPM, OSE

FDA ATTENDEES:

Lisa Khosla, Team Leader, DMEPA, OSE

Jacqueline Sheppard, Safety Evaluator, DMEPA, OSE

Irene Z. Chan, Associate Director, DMEPA, OSE

EXTERNAL ATTENDEES:

John Kim – VP of Quality, Regulatory and Vigilance, Pierre Fabre Pharmaceuticals, Inc. (USA)

Peggy Michel - Regulatory Affairs Project Manager, Pierre Fabre Dermatologie (PFD)

Marie-Laure Vareilles - Head of International Regulatory Affairs, PFD

Jean-Jacques Voisard - General Manager, PFD

Background:

Pierre Fabre submitted the proposed proprietary name, (b)(4) NDA 205410 for a 4.8 mg/ml oral solution on January 14, 2014.

Discussion:

The Division of Medication Error Prevention and Analysis requested this teleconference to discuss the concerns we have regarding the proposed proprietary name, (b)(4), for propranolol hydrochloride. DMEPA finds the name, (b)(4) unacceptable because the (b)(4)

Due to changes in (b)(4), the proposed name (b)(4) had to be resubmitted for review. Since the previous review of (b)(4) in NDA 205410 (OSE RCM# 2013-1269 on August 9, 2013), (b)(4)

(b)(4)

(b)(4)

(b) (4)

Regulatory Options:

- withdraw the proposed proprietary name, (b) (4) and submit a completely new proprietary name or consider an option with (b) (4). Either change will require a withdrawal of the current name and a submission of the request for the review of the new proprietary name.
- wait for the official completed letter denying the proposed proprietary name, (b) (4) which we will finalize on or before March 17, 2014.

Action Items:

Pierre Fabre Pharmaceuticals will let us know as soon as possible which option they prefer.

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/s/

CHERYE D MILBURN
02/06/2014



NDA 205410

INFORMATION REQUEST

Pierre Fabre Dermatologie
Attention: John C. Kim, RPh, JD
Vice President of Quality Assurance, Regulatory Affairs and Vigilance
8 Campus Drive, 2nd Floor
Parsippany, NJ 07054

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Propranolol Oral Solution.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

S.2.2 Description of Manufacturing Process and Process Controls

1. The starting material, (b) (4), and the intermediate, (b) (4), have structural alerts for genotoxicity; provide a rationale for not including a test and appropriate acceptance criterion for them in the drug substance specification.

S.4.1 Specification

2. The IR method is selected as a test for Identification of the drug substance; establish that polymorph (b) (4) is consistently obtained by providing IR spectral overlays of (b) (4) and other polymorphic forms.

S.4.2 Analytical Procedures

3. You state that the reference standard complies with Ph. Eur.; however, it should also comply with the USP. Provide information to show that the standard is USP compliant.

P.2.4 Container Closure System

4. At the pre-NDA meeting of April 26, 2012, the Agency asked if the markings on the oral syringe could withstand multiple washings over the maximum duration of use (e.g., 60 days). Provide this information which is missing in the NDA.

5. Provide DMF references, where applicable, for the packaging components and related LOA.

P.5.1 Specification(s)

6. The acceptance criterion for 'Deliverable Volume' should conform to that stipulated in USP <698> for multiple-unit containers for liquids, where-in the average volume and labeled volume of the containers are considered.
7. Provide an updated drug product specification section.

P.5.3 Validation of Analytical Procedures

8. The system suitability testing, as described in ICH Q2(R1)-Validation of Analytical Procedures (Item 9), is not presented for the Assay method. Conduct this validation study and provide the results.

P.6 Reference Standards or Materials

9. In this section you only provide the specification for the reference standard; the COA of a representative sample of the reference standard should also be submitted.

P.8.1 Stability Summary and Conclusion

10. Provide structural characterization information for the impurity (RRT = (b) (4)) linked to propranolol degradation upon exposure to light in the clear glass bottle.
11. An upward trend in the assay data is evident after 18 months at 25°C/60% RH and 30°C/75% RH for one of the stability batches (SB0796/B – from (b) (4) mg at T0 to (b) (4) at T18) and after 6 months at 40°C/75% RH for all of the stability batches. This trend suggests that the assay may exceed the upper acceptance criterion of (b) (4) on further storage. Based on ICH Q1E-2.4.1.2, *long-term or accelerated data showing change over time and/or variability*, the extrapolated shelf-life should not be more than 6 months beyond the period covered by long-term data. Therefore, your proposal for a (b) (4) month shelf-life based on 18 months' data is not acceptable; however, a shelf-life of (b) (4) months may be granted. You were informed of this issue in the Filing Communication dated July 17, 2013.
12. If available, provide 24 months' stability data.

R2 Methods Validation Package

13. This section is incomplete since you have not provided a listing of samples retained by you for testing by the FDA Laboratory. Submit a complete Methods Validation Package

as recommended in the *Draft Guidance for Industry, Analytical Procedures and Methods Validation, Section X*.

R2A. Labeling

14. Unlike other propranolol hydrochloride solutions currently on the market, we note you have chosen to use the name of the active moiety, propranolol, instead of the name of the salt, propranolol hydrochloride, which conforms to USP <1121>-Nomenclature. Accordingly, you have based the strength of this product on the active moiety, 3.75 mg/mL, instead of the salt. Since there are other propranolol hydrochloride oral solutions on the market, the Agency is concerned with medication errors associated with the products being interchanged. Hence, there is a specific safety concern with the use of the established name based on the active moiety instead of the salt. Accordingly, revert to the salt nomenclature on all labels and labeling (container, carton, insert, etc.). Include the equivalency statement: 4.28 mg/mL of propranolol hydrochloride is equivalent to 3.75 mg/mL of propranolol. Due to our review timeline, please submit revised labels and labeling no later than October 31, 2013.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
10/15/2013



NDA 205410

INFORMATION REQUEST

Pierre Fabre Pharmaceuticals, Inc.
Attention: Mr. John C. Kim
8 Campus Drive, 2nd floor
Parsippany, NJ 07054

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (propranolol) Oral Solution, 3.75 mg/mL.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical/Statistical

1. For Study 201, according to Table 42 of the clinical study report, we noted that the proportion of patients who had “primary efficacy endpoint deviation” was higher in V0400SB dose groups than in the placebo group, as was the proportion of patients who took prohibited concomitant IH medication during treatment period. In particular, the V0400SB 3 mg/kg/day 6 months group had 20.6% of patients who had this type of protocol deviation and 14.7% of them took prohibited concomitant IH medication during treatment period, whereas the placebo group had only 5.5% patients with this type of deviation and 3.6% of them took prohibited concomitant IH medication during treatment period. The deviation about other prohibited treatment intake also showed that all V0400SB dose groups had higher proportions than did the placebo group. Similarly, the V0400SB 3 mg/kg/day 6 months group had a much higher proportion of this type of deviation than did the placebo group (14.7% vs. 3.6%). Please explain why these occurred.
2. For Study 201, according to Table 42 of the clinical study report, we also noted that among 55 placebo patients, 23 of them had some exams not performed. Most of them had at least one NA or one glycemia exam not performed. Compared with V0400SB dose groups, the rate of “exams not performed” was much higher in placebo group. Please explain why this occurred.
3. Your clinical study report states that “the center effect or country effect were not addressed in the statistical analyses.” Since we observed that France had a much higher rate of dropouts in the placebo group than other countries did, and some imbalance occurred in terms of the ratio of patients randomized to study drug and placebo in some countries (e.g., Peru), please provide the details of your randomization procedure, specifically, the detailed plan for patient recruitment in each country.
4. Please provide exploratory analyses to assess any center or country effect for each of the following patient populations:
 - Stage 1 ITT population of 188 patients (for all 5 treatment groups)
 - Stage 2 ITT population for the Placebo and 3mg/kg/day x 6 month treatment groups
 - Pooled patients with overrun for all 460 patients enrolled.

Labeling

We note there are multiple places within the labeling that have expiration date discrepancies. On the bottle label and container labeling, it states that the unused portion should be discarded after (b) (4). However, in the PATIENT INFORMATION under “**How should I store** (b) (4) and in the FULL PRESCRIBING INFORMATION under Section 16.2 **Storage and Handling**, it gives a 2 month expiration date. Please clarify.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
09/03/2013



IND 104,390

INADEQUATE STUDY REQUEST

Pierre Fabre Pharmaceuticals, Inc.
Attention: Mr. John C. Kim
9 Campus Drive
Parsippany, NJ 07054

Dear Mr. Kim:

We refer to your correspondence dated August 29, 2012, requesting that FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for Propranolol Oral Solution.

We reviewed your proposed pediatric study request (PPSR) for study V00400 SB 201 and are unable to issue a Written Request because study V00400 SB 201 is a pivotal clinical study which has been submitted in your New Drug Application (NDA) for (b) (4) (propranolol) Oral Solution, filed on July 16, 2013 (NDA 205-410).

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{ See appended electronic signature page }

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
08/26/2013



NDA 205410

FILING COMMUNICATION

Pierre Fabre Pharmaceuticals, Inc.
Attention: Mr. John C. Kim
8 Campus Drive, 2nd floor
Parsippany, NJ 07054

Dear Mr. Kim:

Please refer to your New Drug Application (NDA) dated May 17, 2013, received May 17, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (propranolol) Oral Solution, 3.75 mg/mL.

We also refer to your amendments dated May 30 and June 21, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 17, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 17, 2014.

Standard Review Classification

We note you requested a Priority review classification and provided the following points in your submission dated May 17, 2013:

- IH requiring systemic therapy is an orphan disease, which can create serious and life-threatening medical complications in small children, including airway involvement, impediment of feeding, ophthalmologic complications often requiring surgery, associated structural anomalies such as cardiac defects, increased risk of visceral involvement, and hepatic lesions including congestive heart failure and hyperthyroidism;
- There is currently no FDA-approved treatment for IH;
- Patients who experience proliferating IH represent a clear unmet medical need;
- (b) (4) specifically formulated and developed for pediatric use;
- Phase 2/3 study with (b) (4) demonstrated statistically significant and sustained clinical improvements in IH patients compared to placebo and a favorable safety profile;

- The magnitude of the treatment effect is clinically relevant and significantly greater than any effects previously reported with historical treatments; (b) (4) stands as a clear leader as a first-line treatment for IH requiring systemic therapy.

We reviewed your request and have classified this application as a Standard review for the following reasons:

You submit that (b) (4) fills an unmet, urgent medical need where no satisfactory alternative therapy exists.

However, corticosteroids, INF alpha and vincristine have been recommended for use by the American Academy of Dermatology's Guidelines¹ for about 15 years. Recently, timolol maleate, a nonselective beta blocker used in ophthalmic solutions to treat glaucoma, has been evaluated as a topical 0.5% or 0.1% timolol maleate gel-forming solution to treat patients with IH.² That none of these therapies has the indication is not considered germane to the decision.

Although we recognize the difficulties with making comparisons of these therapies across trials and differences in endpoints among these studies, we summarize the efficacy and safety information of currently available treatment compared to (b) (4) in Table 1.

Table 1 Efficacy/safety profiles of currently available treatments for Infantile Hemangioma

	Corticosteroids (First line treatment)	IFN alpha (Second line treatment)	Vincristine (Third line treatment)	Timolol (recent topical treatment)	(b) (4) (NDA data)
Efficacy and dose	84% response rate ³ (cessation of growth or reduction in size) Re-growth in 36% at 2.9 mg/kg/day, 1.8 months. ⁴ Inhibits growth rather than reducing IH size.	40-50% complete response. ^{5,6} First signs of regression are usually observed within 2-12 weeks.	Shows a clear response in 7/9 (78%) infants. ⁷ Successful in IH refractory to other therapies with vital structure involvement or associated with KMS. Dose: 1 mg/m2/day for 6 months	72 of 73 patients (median age 4.3 months) improved (response rate = 99%) ^{Error! Bookmark not defined.} Dose: 62 were treated with 0.5% solution and 11 with 0.1% solution for 3.4 ± 2.7 months.	Primary endpoint (complete or nearly complete resolution at 24 weeks) achieved by 61 of 101 patients (Response rate = 60%) ¹¹ Dose: 3 mg/kg/day for 6 months
Safety & Tolerability	Mood changes, insomnia, GI symptoms. Cushingoid face frequent after 1-2 months tx, hypertension, adrenal suppression, immunosuppression, bone demineralization, hypertrophic cardiomyopathy ⁸ , Pneumocystis carinii pneumonia in infants given high doses.	Transient neutropenia, fever, elevated liver enzymes and flu-like symptom. Neurotoxicity including spastic diplegia and motor developmental disturbances may occur in 10 to 30% of cases. ⁹ Motor developmental disturbances resolve in majority, diplegia is largely irreversible. ¹⁰	AEs such as severe constipation and peripheral neuropathy are dose-related and dose-limiting.	Sleep disturbance noted in one patient. Predictors of better response: (i) superficial type of IH (p=0.01), (ii) 0.5% solution (p=0.01), and (iii) duration >3 months (p=0.04).	bradycardia (2 cases), hypotension (5 cases), hypoglycemia (2 cases), asthma (12 cases) and 46 SAEs in 33 patients (including 1 patient with 2 nd degree Mobitz type AV block, 1 with bradycardia/enterocolitis, 1 obstructive bronchiolitis, 1 diabetes mellitus type 1 with ketoacidosis, 1 worsening of hemangioma and 1 ulceration of IH - grade 3).

GI: gastrointestinal; IFN: interferon; IH: infantile hemangioma; KMS: Kasabach-Merrit syndrome; tx: treatment. ³Enjolras et al. 1990; ⁴Bennett et al. 2001; ⁵Frieden et al. 2005; ⁶Ezekowitz et al. 1992; ⁷Enjolras et al. 2004; ⁸Barrio et al. 2005; ⁹Boon et al. 2006; ¹⁰Barlow et al. 1998 {Source: Sponsor's references} ¹¹ Efficacy data in NDA

The response rates obtained with the other available drugs (Table 1) appear to be as good as or better than those obtained with (b) (4) (60%); corticosteroids produce a 84% response rate, INF alpha a 40-50%

¹ Frieden IJ, Eichenfield LF, Esterly NB, Geronemus Rk, Mallory SB, the Guidelines/Outcomes Committee. Guidelines for care of hemangiomas of infancy. *J Amer Acad Derm* 1997;37:631-7.

² Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. *Pediatr Dermatol* 2012;29(1):28-31.

response rate (with regression starting at 2-12 weeks), Vincristine a 78% response rate (in 7 of 9 infants) and timolol a 99% response rate (72 of 73 patients improved).

Although propranolol hydrochloride solution appears to be effective, we cannot be persuaded of its superiority over other available therapy absent a direct comparison.

During our filing review of your application, we identified the following potential review issues:

Product Quality

The amount of stability data submitted in the NDA does not support (b) (4) months expiration dating period for the drug product. The actual duration will be determined after a complete review of the submitted stability data.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Product Quality

Please request the DMF Holder (DMF (b) (4) Holder (b) (4) to submit a LOA to the DMF authorizing FDA to refer to their Master File for information regarding (b) (4) and to provide the missing DMF page 3/3 for their (b) (4) (b) (4).

Microbiology

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43. In order to control for the presence of BCC in your product you should consider the following:

- Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

- As there are currently no compendial methods for detection of BCC, we have provided suggestions for a validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Administrative

Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 16418 for Inderal, but it does not contain a patent certification or statement with respect to this application. Please provide an appropriate patent certification or statement.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL)

GENERAL FORMAT

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 ½ inch margins on all sides.*
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 granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).
Comment: *Please correct.*
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.*
4. 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 bulleted statement under DOSAGE AND ADMINISTRATION.*

HIGHLIGHTS DETAILS

Initial U.S. Approval

5. 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.

Contraindications

6. 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 (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.

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

Comment: Please correct.

Patient Counseling Information Statement

8. Must include the following **bolded** verbatim statement (without quotation marks):

“See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”

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

Contents: Table of Contents (TOC)

GENERAL FORMAT

9. 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.

10. 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

11. 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)].”*

FULL PRESCRIBING INFORMATION DETAILS

Adverse Reactions

12. 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

13. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use the following statement at the beginning of Section 17:

“See FDA-approved patient labeling (Patient Information and Instructions for Use)”.

Comment: *Please correct text to as in the statement above (without quotation marks).*

We request that you resubmit labeling that addresses these issues by August 7, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
07/17/2013



NDA 205410

NDA ACKNOWLEDGMENT

Pierre Fabre Pharmaceuticals, Inc.
Attention: Mr. John C. Kim, RPh, JD
U.S. Agent for Pierre Fabre Dermatologie
Vice President of Quality Assurance
Regulatory Affairs & Vigilance
8 Campus Drive, 2nd Floor
Parsippany, NJ 07054

Dear Mr. Kim:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: May 17, 2013

Date of Receipt: May 17, 2013

Our Reference Number: NDA 205410

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 16, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
05/23/2013



Pierre Fabre
Pharmaceuticals

17 May 2013

Food and Drug Administration
Office of Regulatory Affairs
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **Field Copy for NDA 205-410** (b) (4) **(propranolol) Oral Solution**

Dear Sir or Madam:

On behalf of Pierre Fabre Dermatologie, a foreign applicant located in Boulogne, France, please refer to New Drug Application (NDA) 205-410 for (b) (4) (propranolol) 3.75mg/mL Oral Solution for the treatment of proliferating infantile hemangioma requiring systemic therapy.

The NDA dossier for (b) (4) is being submitted concurrently in electronic Common Technical Document (eCTD) format to the Division of Cardiovascular and Renal Products within the Center for Drug Evaluation and Research.

In accordance with 21 CFR 314.440(a)(4), a duplicate field copy is not provided as the Office of Regulatory Affairs should have access to the technical section of Module 3 containing the chemistry, manufacturing and controls for the (b) (4) NDA.

Should you have any questions regarding this submission, please do not hesitate to contact me at (973) 647-1640 or via email at jkim@pfpharmausa.com.

Sincerely,

John C. Kim, RPh, JD
Vice President of Quality Assurance,
Regulatory Affairs and Vigilance
US Agent for PIERRE FABRE DERMATOLOGIE

Pierre Fabre Pharmaceuticals, Inc. - 8 Campus Drive - Parsippany, NJ 07054
Tel. (973) 647-1600 Fax (862) 207-7077

1.3.2 Field Copy Certification

In accordance with FDA Guidance for Industry: *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* dated June 2008 and in compliance with 21 CFR 314.50(d)(1)(v), a field copy is not be provided to the FDA Office of Regulatory Affairs District Office as the NDA is in electronic Common Technical Document format.

Since Pierre Fabre Dermatologie is a foreign applicant, a field copy notification letter is submitted to the Office of Regulatory Affairs in accordance with 21 CFR 314.440(a)(4) to the address described in (a)(1) of the section. A copy of this letter is attached.



John C. Kim, RPh, JD
Vice President of Quality Assurance,
Regulatory Affairs and Vigilance
US Agent for PIERRE FABRE DERMATOLOGIE

17 May 2013
Date :

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	<h2 style="margin: 0;">PRESCRIPTION DRUG USER FEE COVERSHEET</h2>
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A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

1. APPLICANT'S NAME AND ADDRESS PIERRE FABRE PHARMACEUTICALS INC JOHN KIM 9 CAMPUS DR PARSIPPANY NJ 07054408 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 205-410
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 973-647-1640	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME (b) (4) (Propranolol)	6. USER FEE I.D. NUMBER PD3013308
--	--------------------------------------

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? YES NO
 PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
 A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
 THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
 THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
 If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:
 Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	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.
---	--	--

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE John C. Kim	TITLE VP of Quality Assurance Reg Affairs & Vigilance	DATE 04/24/2013
--	---	--------------------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 (b) (4)



IND 104390

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pierre Fabre Dermatologie
c/o Voisin Consulting, Inc
675 Massachusetts Ave.
Cambridge, MA 02139

ATTENTION: Cécile De Coster, M.Sc.
Director, Voisin Consulting, Inc. Life Sciences

Dear Ms. De Coster:

Please refer to your Investigational New Drug Application (IND), submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for propranolol hydrochloride oral solution.

We also refer to your April 24, 2012, correspondence, received April 25, 2012, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable. However, this decision is based on the current proposed indication of use, proliferating infantile hemangiomas requiring systemic therapy. If your future development program includes expansion of the currently proposed indication of use, we will find the proposed name (b) (4) unacceptable. Expanding the proposed name to other indications of use would misleadingly imply that the product treats only hemangiomas.

A request for proprietary name review for (b) (4) should be submitted once the NDA is submitted. Additionally, if **any** of the proposed product characteristics as stated in your April 24, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact, Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager,

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
10/11/2012



IND 104390

MEETING MINUTES

Cortney Mills, M.Sc., RAC
U.S. Agent for Pierre Fabre Dermatologie
Voisin Consulting, Inc.
675 Massachusetts Ave.
Cambridge, MA 02139

Dear Ms. Mills:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for propranolol hydrochloride oral solution.

We also refer to the meeting between representatives of your firm and the FDA on April 26, 2012.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Dan Brum, Pharm.D., BCPS, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

{ See appended electronic signature page }

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

- meeting minutes
- sponsor's slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 26, 2012 @ 10 a.m.
Meeting Location: White Oak Bldg 22 Room 1315

Application Number: 104390
Product Name: propranolol oral solution
Indication: proliferating infantile hemangiomas
Sponsor/Applicant Name: Pierre Fabre Dermatologie

Meeting Chair: Norman Stockbridge
Meeting Recorder: Dan Brum

FDA ATTENDEES

DCRP: Norman Stockbridge (Director), Khin U (clinical), Tom Papoian (nonclinical team leader), Al DeFelice (nonclinical team leader), Elizabeth Hausner (nonclinical), Dan Brum (regulatory project manager)

Office of Clinical Pharmacology: Divya Menon-Andersen (clinical pharmacology reviewer)

Office of Biometrics I: Yeh-Fong Chen (statistics)

ONDQA: Kasturi Srinivasachar (lead), Thomas Wong (reviewer)

OPS (microbiology): Erika Pfeiler

OSE/DMEPA: Kellie Taylor (deputy director), Forest "Ray" Ford (reviewer)

Office of the Commissioner, Office of International Programs: Heidi Janssen (EMA Fellow)

SPONSOR ATTENDEES

Attendees from Pierre Fabre

- Marie-Laure Vareilles, Regulatory Affairs Director
- Christine Chaumont, Development Project Director
- Mireille Basquin, CMC Quality Control
- Jean-Jacques Voisard, Dermatologist, Head of Pierre Fabre Dermatologie
- Natasha Nelson, Esq., VP of Compliance and Head of Regulatory Affairs Pierre Fabre USA
- Alain Delarue MD, Head of Therapeutic Area - Internal Medicine

By Phone

- Françoise Fraboul MD, Nonclinical Expert
- Marie Bourgeois, CMC Project Manager

- Anne Lappereau-Gallot, M.D, Head of Corporate Vigilances –Internal Medicine
- Valerie Brunner, Head of Pharmacokinetics
- Pascal Lefrançois, Head of Dermatology Division

Consulting Team on behalf of Pierre Fabre

- [REDACTED] (b) (4)
- Cortney Mills, US Regulatory Consultant, Voisin Consulting Life Sciences
- Laura Mondano, US Regulatory Consultant, Voisin Consulting Life Sciences

BACKGROUND

Pierre Fabre Dermatologie (the sponsor) is developing propranolol oral solution (V0400SB) 3.75 mg/mL for the treatment of proliferating infantile hemangiomas requiring systemic therapy. The sponsor plans to submit a New Drug Application (NDA) for propranolol hydrochloride oral solution in accordance with Section 505(b)(2) of the Federal Food, Drug & Cosmetic Act for the treatment of proliferating IH requiring systemic therapy in December 2012.

Regulatory History

- September 5, 2008: Orphan designation (08-2667)
- January 31, 2009: Parallel Scientific Advice Meeting with sponsor and EMA
- July 1, 2009: new IND submitted
- August 19, 2009: clinical Special Protocol Assessment (SPA) submitted
- October 2, 2009: SPA *no agreement* letter sent to sponsor
- November 10, 2009: Type A meeting with sponsor re: SPA
- May 21, 2010: Type C teleconference with sponsor
- [REDACTED] (b) (4)

The purpose of this meeting was to discuss to the adequacy of the quality, nonclinical, and clinical data package for the expected December 2012 NDA submission. The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below; preliminary responses are in **bold, black font**, and **bold, green font** reflects the main discussion points during the meeting. Note the sponsor submitted responses to the preliminary responses via email on April 25, 2012 and also presented a back-up slide during the meeting (attached).

REGULATORY

1. Does the FDA agree that an NDA in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act is appropriate?

Preliminary response:

A 505(b)(2) application would be an acceptable approach at this time, provided the regulatory requirements for a 505(b)(2) application are met. For sponsors considering the submission of an application through the 505(b)(2) pathway, the division recommends consulting the Agency’s regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)”

available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

Also please note the following information regarding the submission of an application through the 505(b)(2) regulatory pathway.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Please note that if you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) as the comparator (rather than, for example, a bioequivalent ANDA product).

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative BA study, you should use the ANDA product designated as the RLD in the Orange Book as the comparator in a comparative clinical trial to establish a bridge

between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA’s finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on a finding that the drug was not discontinued for reasons of safety or effectiveness.

You propose to reference information from the Summary Basis of Approval (SBA) or FDA reviewers’ public summaries for support of safety and/or efficacy. We note that a 505(b)(2) applicant that seeks to rely upon the Agency’s finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the FD&C Act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Meeting: Little was resolved in the meeting. Upon further consideration, the Division notes the following:

The sponsor provided pharmacokinetic data on pages 21 (Study V00400SB101 2A) and 23 (V00400SB102) of the meeting package. The sponsor also provided the excipients of the referenced EU tablets (Appendix 6).

We think the proposed two-step “bridging” program described on slide 6 (enclosed) is an acceptable approach; acceptability of the data will ultimately be a review issue.

Sponsor’s proposed bridging program:

- 1. In vivo Bioavailability (BA)
Comparable BA of V0400SB and EU Propranolol tablets (Avlocardyl®) demonstrated in 12 healthy adults**
- 2. In vitro Dissolution Test
Similar dissolution profiles of Avlocardyl® 40 mg and Propranolol HCl USP 40 mg (Barr/TEVA) tablets**

QUALITY

2. Does the FDA agree that the two proposed presentations (bottle and graduated oral syringe measuring device) are appropriate?

Preliminary response:

You propose to market (b) (4) net quantity bottles, (b) (4) and 120 mL, each with a single oral syringe. Considering the usual growth patterns for infants, we expect wide variability in volumes required for dosing this product throughout the

three to six month treatment duration. [REDACTED] (b) (4)

[REDACTED] **Additionally, given the variability in dosing, you should consider the possibility that not all patients will receive a full bottle of solution. If this were to occur, it is unclear how additional patients will obtain the required dosing device if a single device is provided with each bottle.**

You propose to market [REDACTED] (b) (4) 5 mL, to accommodate the full dosing range for this product. [REDACTED] (b) (4)

[REDACTED] (b) (4) **we recommend you explore a single net quantity packaging configuration with [REDACTED] (b) (4) The net quantity chosen should take into consideration a) the expected dispensing volumes sufficient for a 30-day supply, b) a bottle size that will allow for easy withdrawal of the prescribed dose, and c) the avoidance of excessively large volumes that can result in waste of drug.**

Regarding our suggestion to include a packaging configuration [REDACTED] (b) (4), we think such a presentation would necessitate that a caregiver exercise judgment regarding the appropriate device to choose to administer a dose. If you have evidence to support the capability of caregivers to determine the appropriate device to use and their ability to withdraw doses accurately, please include this information in your NDA submission.

In addition, [REDACTED] (b) (4) do not include a statement indicating the product is for "[REDACTED] (b) (4)" which introduces vulnerability for wrong route of administration medication errors to occur.

The acceptability of any proposed product presentation is subject to review.

Meeting: The sponsor clarified that the bottle is fitted with a fixed adapter inserted into the neck of the bottle; therefore, the to-be-marketed bottle is intended to be dispensed in its entirety and pharmacists would not be able to dispense partial quantities.

The sponsor plans to market a single 5 mL syringe. [REDACTED] (b) (4)

There was no further discussion on this issue.

The sponsor acknowledged DMEPA's [REDACTED] (b) (4)

DMEPA asked if the markings on the oral syringe could withstand multiple washings over the maximum duration of use (e.g., 60 days). The sponsor planned to follow-up on this issue.

The sponsor acknowledged that the precision and accuracy data from the 5 mL oral syringe performance tests used drug product and not water.

The sponsor does not plan to conduct a usability study and DMEPA agreed that one is not needed.

3. Does the FDA agree with the removal of the [REDACTED] (b) (4), in the commercial formulation based on the data provided?

Preliminary response:

Yes, the studies described are adequate to support the removal of the [REDACTED] (b) (4) [REDACTED] (b) (4) from the formulation for the drug product.

No discussion

4. Pierre Fabre plans to include the process validation protocol and supportive data on 3 industrial batches in the NDA submission. The validation batches will be manufactured before the Pre-Approval Inspection (PAI). Does the FDA agree with the planning of the validation batches?

Preliminary response:

The Agency does not currently require validation of the proposed commercial manufacturing process prior to the approval of the NDA. Additionally, FDA does not approve process validation approaches, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria, and study outcomes will be evaluated during an inspection. It is, however, the expectation of the Agency that Stage 2 Process Validation should be completed prior to the decision to release product for commercial distribution.

From a microbiological perspective, the data provided from the three production batches are expected to be adequate for us to conduct our review.

No discussion

5. The proposed specifications for the drug product release and stability testing has been established according to ICH guidelines and FDA guidance's and has been justified by data generated from development batches. Does the FDA agree with the selected quality

attributes for drug product testing? Does the FDA agree with the acceptance criteria selected?

Preliminary response:

Yes, the selected quality attributes for the drug product are acceptable. However, a final decision on the acceptance criteria will be made as part of the NDA review based on the justification and data submitted.

No discussion

6. Pierre Fabre plans to verify the uniformity of mass of delivered doses from the oral syringe according to EP 2.9.27. Does the FDA agree that this test will be performed with water as quality control of the measuring device (oral syringe) to ensure performance of the device for drug delivery?

Preliminary response:

No. The use of water for the test does not reflect the accuracy of dose delivery of the actual propranolol solution. A small change in density, viscosity, or surface tension of the commercial oral solution may affect the accuracy of volume measurement of the solution, thus affecting the accuracy of dose delivery. The test will need to be performed with the to-be-marketed drug product.

The microbiological specifications and associated acceptance criteria are adequate.

No discussion

NONCLINICAL

7. Based upon the described nonclinical data, does the FDA agree that the proposed nonclinical safety package is sufficient for registration of V0400SB in the treatment of IH?

Preliminary response:

Please see the information provided in the response to question 1 regarding submission of an application through the 505(b)(2) pathway.

The published data for Inderal do not provide information about whether or not the drug has any effect on post-natal growth and development. Further, the reference provided used an age group of rat that did not correspond to the proposed infant patient population, and did not examine the endpoints usually assessed in post-natal development studies (e.g., long bone measurements, learning and memory, and reproductive ability). Please discuss the available published literature and any additional plans for determining potential effects on post-natal growth and development, including reversibility of any effects.

Meeting: Dr. Hausner said beta₂-adrenergic receptors are prevalent on ovarian tissue and there are some reports in the literature investigating use of beta blockers for various ovarian problems of women. Given this concern, the sponsor was asked how

they intended to address the potential developmental concern of propranolol use in infants. The sponsor discussed a proposal to evaluate post-natal development in juvenile rats with the following endpoints: long bone measurements, learning and memory, and reproductive ability (histology of reproductive organs). Dr. Hausner said that in addition to providing histology data, the sponsor should study the functional effects on reproduction, which could be done as an extension of the sponsor's proposed study. Drs. Hausner and Papoian agreed to engage in further discussion about this issue (e.g., teleconference with the sponsor) and to review a future draft protocol.

Does the FDA agree that a simple reference to the Inderal NDA SBAs is sufficient for the V0400SB NDA without further detailed information on the nonclinical studies contained within those Inderal applications?

Preliminary response:

Your proposal to rely on the Inderal NDA SBAs to support the safety and efficacy of your proposed 505(b)(2) application is not acceptable. As stated above, a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

No discussion

CLINICAL

8. Does the Agency agree that this data would be supportive to the overall evaluation of the safety profile of V0400SB in the treatment of IH and should be included in the NDA?

Preliminary response: Yes, the safety data collected from the ATU (Nominative Temporary Authorization for Use) of the compassionate use program ongoing in France should be included in the NDA as supportive data.

Please note that the Division prefers that >1000 (ICH requires 1,500) patients from the intended population for “the treatment of infantile hemangiomas requiring systemic therapy,” namely infants, be studied in pivotal trials and followed for 1 year for safety. We suggest that you obtain the safety data and analyses of cases in the literature and short and long-term sequelae such as recurrence, scarring, etc., and create case report forms (CRFs) to enable appropriate statistical analyses.

The adequacy of sample size for the NDA for safety is contingent upon the quality and adequacy of safety data from (i) the 460 infants followed for 18 months after the end of treatment in the pivotal trial, (ii) the children (projected number =16) who existed clinical studies V00400SB102 and V00400SB201 and were enrolled into clinical study V00400SB301 and continued open-label oral propranolol solution treatment, (iii) the 367 patients who were included in a compassionate use program in France and Switzerland, and (iv) the cases of infantile hemangiomas treated with oral propranolol solution reported in the literature to date.

Meeting: The Division and sponsor agreed not to pool analyses from studies V00400SB201 and -102 because of different timepoints for efficacy evaluation.

Dr. Stockbridge said the sponsor's proposal for the safety database seemed reasonable and could *potentially* be adequate depending on the quality of the data; however, no final determination was made.

Regarding the Division's request that the sponsor create CRFs from the AE cases reported in the literature, the sponsor said it was not feasible and would not add value to the analysis given the relative lack of completeness of those CRFs. The Division acknowledged the sponsor's comment and suggested that at a minimum the sponsor try to include information about the duration of treatment, location of the lesion, and age of the patient. The Division stated that in addition to the sponsor's narratives of these literature cases, the sponsor should also provide documentation of these cases with reprints of the case reports in their original form (in the original language they were published).

Dr. Menon-Andersen requested that the sponsor submit electronic datasets for study V00400SB102.

Does the FDA agree on the placement of the analysis and periodic safety reports of the foreign data derived from the named patient program in Module 2.7.4.6 Post-Marketing Data and Module 5.3.6 Reports of Post-Marketing Experience, respectively?

Preliminary response: Yes

No discussion

Does the FDA agree that submission of CIOMS forms for non-serious cases reported from the compassionate use program in the NDA is not required?

Preliminary response: Yes

No discussion

LABELING

9. V0400SB requires an initial dose titration in order to achieve the recommended starting dose. Pierre Fabre proposes to include a conversion table, based upon patient weight, in the Prescribing Information (PI) to assist physicians with an accurate dose titration. Does the FDA agree that a titration table in the PI would be useful and appropriate for the prescribing physician?

Preliminary response:

DMEPA is not opposed to the inclusion of a dosing table provided the table is not vulnerable to confusion that can lead to medication error. As currently proposed, the titration table may be vulnerable to confusion for the following reasons:

- 1. The table has trailing zeros which can be a source of error resulting in an incorrect dose. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter or tube sizes.**
- 2. The table contains multiple units of measure (kg, mg, and mL). To minimize the risk of confusion, consider combining the two columns titled “dose per intake” into a single column and reporting the dose as follows:
e.g., 2 mg (0.5 mL)**
- 3. There is a discrepancy between the mL doses listed in the table and the actual mL doses calculated based on weight. It appears that the doses in the table have been rounded to the nearest 0.1 mL. If your studies support doses rounded to the nearest 0.1 mL in this population, then a statement should be added to the Dosage and Administration section of your insert indicating that calculated doses should be rounded to the nearest 0.1 mL.**
- 4. The table does not account for a complete weight range, and it is unclear how to dose patients who fall between the listed weight categories. The weights in the proposed table increase by increments of 0.5 kg; however, many patients will not fit neatly into these weight increments. It is unclear if providers should round patient weights to the nearest 0.5 kg or whether there are other factors that should be considered prior to dosing.**
- 5. Having a column titled “(b) (4)” underneath a statement of dose in (b) (4) can be confusing. This may result in the provider further dividing the volume listed in the (b) (4)” column, believing that is the total daily dose. To improve clarity, remove any reference to dose in (b) (4) y from the table (remove the second row from the table) and consider retitling the column “(b) (4)” to read “dose administered twice a day”.**

No discussion

- 10. Pierre Fabre has provided a target Prescribing Information text for V0400SB in the treatment of IH. Pierre Fabre requests FDA feedback on the draft contents of the PI based upon the design of the pivotal phase 2/3 study, as well as the known pharmacokinetic data, nonclinical information and quality data package. Does the FDA agree that the proposed PI can be considered a reasonable product profile at this stage of development?**

Preliminary response:

We will provide specific comments on the content and format of the draft labeling after you submit the NDA; however, we do have the following comments. While we

acknowledge the “target prescribing information text” you provided is in an early draft form, in general, your proposal does not reflect the regulations pertaining to labeling or to FDA guidance documents providing recommendations about the format and content of labeling (also see section entitled “Prescribing Information” below).

In addition, we suggest you exclude information from the labeling that is based solely on the listed drug where such information is not relevant to the indication and patient population studied under IND 104390. Also, please exclude sections and subsections that are both optional and not applicable (e.g., Drug Abuse and Dependence, Microbiology, Pharmacogenomics).

In general, the labeling language will depend on the findings in the NDA including the efficacy and safety results of the pivotal trial, and the safety data in the open-label rollover study, the compassionate use study and any prospective data collected in case reports in the literature.

No discussion

QUESTIONS PROPOSED FOR RESPONSE IN WRITING

Pierre Fabre proposes to receive responses to the following questions in writing:

11. The ICH E3 Guideline for Industry Structure and Content of Clinical Study Report (July 1996) indicates that the placement of Case Report Forms (CRFs) for clinical study reports (CSR) should be in Appendix 16.3 of the corresponding CSR in Module 5 and Section 16.2 (Patient Data Listings) of the CSR should contain all information found in the CRF.

Does the FDA require submission in the NDA, the CRFs for SAEs and Adverse effects Drop Out (ADO) in the Appendix 16.3 of each CSR?

Preliminary response: Yes. In addition to including the CRFs for patients who died or experienced SAEs, please include the CRFs for all patients who discontinued from the pivotal trial for any reason. Include in the CRFs all documents containing clinical information regarding the patients, e.g., SAE worksheets, FAX coversheets with clinical information, clinical data queries, and other documents or communications for completing CIOMIS or Medwatch reports are all part of the CRFs.

Does the FDA agree that in Section 16.4 (Individual Patient Data Listings) of the CSR, it is acceptable to make reference to the Appendix 16.2 (Patient Data Listings) where this information is detailed? If not, Pierre Fabre requests FDA feedback on the requirements for Individual Patient Data Listings.

Preliminary response: Yes.

12. Does the FDA agree that the integration of the narrative part of ISS and ISE in Module 2.7.3 and 2.7.4 is appropriate?

Preliminary response: Yes, the narrative (text) part of ISS and ISE can be submitted in Summary Module 2.7.3 and 2.7.4. The complete set of figures, tables, appendices

and datasets must be submitted in Module 5.3.5.3.

13. Does the FDA agree that the NDA for V0400SB will likely qualify for priority review?

Preliminary response:

Because the review classification is based on conditions and information available at the time the application is filed, a review classification determination cannot be made at this time.

We encourage you to document why you think we should grant this NDA a Priority Review at the time you submit the NDA. Please include any such request with your rationale in Module 1 (Cover Letter) of the NDA.

As a reminder, MAPP 6020.3 entitled “Review Classification Policy: Priority (P) and Standard (S)” includes the following definition for Priority review:

Priority (P) review — Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies. Significant improvement is illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation. Although such evidence can come from clinical trials directly comparing a marketed product with the investigational drug, a priority designation can be based on other scientifically valid information.

14. Does the FDA agree that a claim of categorical exclusion from the requirements of 21 CFR 25.31 for an Environmental Risk Assessment would be feasible for V0400SB NDA?

Preliminary response: Yes, with the statement indicating that the expected introduction concentration (EIC) at the point of entry into the aquatic environment is below 1 part per billion (ppb)/day limit. Also indicate that to the best of your knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

15. Does the FDA agree that paper copies of the NDA are not required, and that the proposed plan to transition the V0400SB documentation to eCTD format?

Preliminary response: The upcoming NDA (in eCTD format) should be complete upon submission. We discourage you from cross-referencing paper documents under IND 104390 because it will reduce the efficiency of review of the NDA; instead, include any such documents in the upcoming NDA submission.

Additional comments:

Include all CRF data available in electronic form in the SAS datasets, e.g., if an electronic CRF (eCRF) system was used, the datasets should include all data in the CRFs. In addition submit the following datasets:

- **A dataset providing the original and final investigator verbatim terms for any AEs or event descriptions that the investigators changed or deleted.**
- **If an eCRF system was used, submit the audit trail of changes to the eCRFs.**
- **A dataset documenting the CEC actions, e.g., dates of adjudication package submissions and adjudicator actions, original adjudications by adjudicator, final adjudication.**

Please submit a table listing all of the tables and figures featured in the main Clinical Study Report of the phase 2/3 trial. The table should contain the following:

- **title of the table or figure in NDA**
- **a page number hyperlink to the location of table or figure**
- **a name hyperlink to the SAS code (and/or macros) used to create the table or figure**
- **names of the datasets used to create the table or figure (a hyperlink is useful, but not necessary)**

Please submit a full list of all relevant communications with respect to this development program including copies of the original protocol, amendments, statistical analysis plan, DSMB charter, CEC charter, and CEC directions and all amendments to them. Please submit copies of all DSMB, CEC, and executive committee minutes and all presentations, letters, newsletters, or site manuals sent to investigators.

Also, please include all photographs from all patients in the trial, including documentation of the nature and position of lighting and photographic equipment used, how the date-stamped photographs were evaluated in a blinded manner, and how disagreements between the blinded assessors were resolved.

For patients who withdrew consent, the details of withdrawal of consent should be documented, i.e., to treatment, to continuing visits, to continuing phone contacts, to provider contacts, and to all contacts. For patients who withdrew consent to treatment but who allow follow-up, the follow-up should be documented well as described for all patients.

When you submit the NDA, please include the following:

- **all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report**

- a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived
- the programs that produced all efficacy results and the programs by means of which the derived variables were produced from the raw variables

Please check the FDA website for information about study data specifications:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

We encourage you to submit a formal meeting request for a “top-line” results meeting at least 2 months prior to the planned NDA submission date.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
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- 1.
- 2.

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
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- 1.
- 2.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Nonclinical study design (see meeting minutes).

4.0 ACTION ITEMS

There are no action items from the meeting.

5.0 ATTACHMENTS AND HANDOUTS

There was one handout (sponsor's slides).

Additional information requests that were emailed to the sponsor on April 20, 2012:

1. *Clinical Pharmacology Summary Aid*
2. *Office of Scientific Investigations Pre-NDA site selection information request*

32 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DANIEL BRUM
05/09/2012

NORMAN L STOCKBRIDGE
05/09/2012



IND 104390

ADVICE/INFORMATION REQUEST

Catherine Bernard, Ph.D.
U.S. Agent for Pierre Fabre Dermatologie
10626 Wagon Box Way
Highlands Ranch, Colorado 80130

Dear Dr. Bernard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for propranolol hydrochloride oral solution.

We also refer to your August 18, 2009 request for a special protocol assessment of a clinical protocol entitled "A randomized, controlled, multidose, multicentre, 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)"; our SPA response letter dated October 2, 2009; your request for a Type A meeting and the minutes of that meeting dated November 16, 2009; your revised clinical SPA dated December 9, 2009; our SPA response letter dated January 7, 2010; your correspondence dated January 22, 2010; our letter dated April 5, 2010; and your amendment dated December 14, 2010.

We have completed our review of your submission dated December 14, 2010, and we have the following comments and requests for information:

Your simulation results regarding control of the type I error rate in the proposed adaptive design was based only on the assumption of a 10% success rate in the placebo group. With only 18 placebo patients at the end of Stage 1, the validity of results obtained by (b) (4) statistics are questionable, more so if the success rate is less than 10%. Please submit your simulation program so we can review your simulation results.

If you have any questions or concerns, please contact Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Pierre Fabre Dermatologie
Attn: J.J. Voisard, MD, Head of Development
45 place Abel Gance
92100 Boulogne, France

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

/s/

NORMAN L STOCKBRIDGE
01/21/2011



IND 104390

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We also refer to your August 18, 2009 request for a special protocol assessment of a clinical protocol entitled "A randomized, controlled, multidose, multicentre, 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)"; our SPA response letter dated October 2, 2009; your request for a Type A meeting and the minutes of that meeting dated November 16, 2009; your revised clinical SPA dated December 9, 2009; our SPA response letter dated January 7, 2010; and your correspondence dated January 22, 2010.

We have completed our review of your submission dated January 22, 2010, and we have the following comments and advice:

1. In addition to the primary endpoint, you have proposed to test two key secondary endpoints: 1) success rate based on the investigator on-site qualitative assessment of complete resolution of the target IH at W48 and 2) time to first sustained improvement. Please note that we remain concerned about the acceptability of the second key secondary endpoint, time to first sustained improvement, since it incorporates subjective assessments such as color change (see #7 below).

To control the overall type I error rate for the primary endpoint and the two key secondary endpoints, you have proposed to use the Hochberg procedure for testing the two key secondary endpoints at the one-sided significance level of 0.005. Since there is a possibility that two doses will be brought forward after Stage 1, assuming that you have two acceptable key secondary endpoints, testing these secondary endpoints by the Hochberg procedure using $\alpha=0.005$ for two winning doses individually may inflate the overall type I error rate.

We would also like to emphasize that since you may (b) (4) the 2nd stage even though your key secondary endpoints will only be tested after winning on the primary endpoint, it is not clear what will be claimed when the dose on which the key secondary endpoint wins differs from the dose on which the primary endpoint wins. In addition, it is unclear whether the unconditional study-wise type I error rate will be controlled even if the type I error rate conditional on the interim decision of either bringing one dose or bringing two doses to the 2nd stage, respectively, is controlled. The entire procedure is very complex because of multiple endpoints and multiple doses with interim analysis. Therefore, in addition to the multiple endpoints, you need to provide a detailed plan for dealing with multiple doses. You should justify the validity of your proposed procedure in terms of controlling unconditionally study-wise type I error rate.

2. You would need to provide the detailed plan for sample size reassessment, which should include when and how the sample size will be increased during the protocol planning stage, even though you indicated that the chance of increasing patients randomized to each treatment arm in the second stage is low. In addition, you should also describe the standard operating procedures for trial logistics and establishment of the firewalls, and how trial integrity is to be maintained for pre-specified interim adaptations.
3. You stated that in Section 3.4 Interim analysis of the Statistical Analysis Plan that “After reviewing the data, the IDMC will choose to either stop the study for safety or futility (all $p > .3$), or continue with the placebo arm and one or two ‘best’ regimens of propranolol, where the ‘best’ regimen is defined as the most efficacious of all regimens with a good safety profile (the safety profile will be evaluated by the two clinicians in the IDMC based on the data available to them at the interim analysis).” Based on the ‘best’ rule, there should be only one regimen from four regimens to be selected based on the interim analysis. If there are differences in opinions on the safety profile between the two clinicians, what will be the rules for making the recommendation by the IDMC? Given these concerns, we note that the IDMC plays an important role to provide recommendations on whether and how the trial will continue based on interim efficacy and safety data, which does not seem to be consistent with what you described in Section 3.5. Please clarify. Also see our response to Question #2.
4. In the interim analysis section, you stated that “a second regimen will only be chosen for further study if the first stage of the study suggests that recruitment in the second stage will be compromised by a 1:1 randomization ratio.” It is unclear what is meant for selection of the second regimen. You also stated that “if one or two regimens are selected at the interim analysis, balanced randomization will then continue to the selected regimen(s) and placebo until a total of 94 patients (85 evaluable) have been randomized to each of these arms over the two phases of the study.” It appears, in the latter statement, that the second regimen when selected will use balanced randomization, which is not about a compromised recruitment issue. For confirmatory trials, the randomization ratio should be pre-specified. Please clarify.
5. In order to control the study-wise type I error rate by using Posch et al. method, we note that you plan to submit a new procedure for dealing with the time to sustained

improvement key secondary endpoint in conjunction with another key secondary endpoint in your proposed design with an interim analysis. Please note again that the current proposed time to first sustained improvement is not an acceptable key secondary endpoint. If you plan to propose another secondary endpoint, you need to include your new procedure in the revised SAP. We would like to remind you that once the trial has been initiated, any major change in the planned statistical procedure will place the integrity of the trial at risk.

6. The IDMC appears to be unblinded; therefore, we would find questionable any role they would play in altering the study sample size. If the IDMC monitors treatment differences, this would be problematic unless such monitoring was limited to the first part of the study only.
7. The secondary endpoint, time to first sustained improvement, would likely not be included in labeling since it incorporates subjective assessments such as color change. You should not spend any alpha on this endpoint.

If you have any questions or concerns, please contact Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Pierre Fabre Dermatologie
45 place Abel Gance
92100 Boulogne, France

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104390	ORIG-1	PIERRE FABRE DERMATOLOGIE	PROPRANOLOL HCL ORAL SOLUTION

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/s/

NORMAN L STOCKBRIDGE
04/05/2010



IND 104,390

**SPECIAL PROTOCOL ASSESSMENT –
NO AGREEMENT**

Catherine Bernard, Ph.D.
U.S. Agent for Pierre Fabre Dermatologie
10626 Wagon Box Way
Highlands Ranch, Colorado 80130

Dear Dr. Bernard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for propranolol hydrochloride oral solution.

We also refer to your August 18, 2009 request for a special protocol assessment of a clinical protocol entitled “A randomized, controlled, multidose, multicentre, 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)”; our SPA response letter dated October 2, 2009; your request for a Type A meeting and the minutes of that meeting dated November 16, 2009; and your revised clinical SPA dated December 9, 2009.

We have the following comments and questions on your revised protocol:

1. You did not submit the case report forms for the entire study. In particular, we are interested in understanding the adjudication details. If you submit a marketing application, we will request that you provide those cases where there was discrepancy between two evaluators. Please make an effort to track that information.
2. We recommend that the data that are generated and recorded be kept on-site in a contemporaneous manner. Thus, the baseline photographs should be stored at the individual sites and not merely collected on a disk after the child completes the study.
3. The key secondary endpoints are coded success/failure (binary endpoint) based on the investigator’s qualitative assessment of complete resolution of the lesion. This metric is currently defined by the on-site investigator. Why isn’t this metric also placed under the purview of the blinded committee? The definition is an all or none metric. Do you supply the minimal change that would be considered a failure?

4. It is unlikely that any of your other secondary and exploratory endpoints would be included in labeling. We do not consider a change in color as reflecting a meaningful benefit. We are interested in how fast the mass of the IH decreases. Furthermore, this metric would not be performed by a central adjudication committee. You may wish to hierarch these endpoints so that if the study succeeds on its primary and secondary endpoints, there is some possibility for a few of these tertiary endpoints to be included in labeling.
5. If your concern is willingness of parents to enroll their children if the option is a 50-50 chance to be placed on placebo, you could impose a 1:2 (placebo:treatment) algorithm to obtain the same willingness to participate.
6. There will be a large number of children enrolled between the first cohort (35/group) and the decision as to what dose(s) to carry forward. We believe the decision as to what dose to carry forward could be tainted by knowledge of the results. Please explain how you will guarantee that the available data from these subjects will not be included in the decision to carry a given dose forward.
7. Is the pipette used to administer the drug to children currently marketed (i.e., generally available)?
8. Is there a plan to down-titrate propranolol at the end of the study? If not, is the recommendation to discontinue the drug abruptly based on data that abrupt discontinuation is not a problem in children?
9. On page 53/112 you have criteria that would require holding or discontinuing blinded therapy. Some of the criteria require a sustained bradycardia for > 1 min. Since rhythm strips are for < 1 min, how do you plan to implement these criteria?
10. You added a futility boundary ($p > 0.3$) in the planned interim analysis. As we discussed during the meeting on November 10, 2009, because interim analyses are generally considered unreliable, a decision to stop the trial early must be made cautiously, particularly if the futility stopping rule is relatively liberal. We recommend that you choose a futility boundary such that the statistical power is not severely compromised.
11. The primary endpoint and one of two key secondary endpoints will be based on complete resolution of the target IH from baseline to Week 24 and Week 48, respectively. When patients drop out before Week 24 or Week 48, according to your plan, they will be treated as failures. In a trial of 48 weeks duration with subjects that are infants, several dropouts are likely, particularly in the placebo group. When the primary endpoint is a binary endpoint and responders will be determined mainly based on the patient's improvement at the last time point, the impact of dropouts on the interpretation of the primary endpoint analysis can be very serious. We recommend that you propose more sensitivity analyses for dealing with dropouts. Also, a statistical method that can incorporate all the observed data (i.e., before patients dropout) should be considered. In this case, continuous variables may be more sensitive than binary variables in detecting a treatment difference.

Therefore, to support the primary endpoint when the dropout rate is high, sensitivity analyses based on some continuous variable versions of this primary endpoint are also recommended.

12. In the statistical analysis plan, you need to provide details of the primary analysis, including a proper multiple comparison adjustment method for the overall type I error rate to incorporate the analysis of the two planned key secondary endpoints.

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104390	ORIG-1	PIERRE FABRE DERMATOLOGIE	PROPRANOLOL HCL ORAL SOLUTION

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/s/

NORMAN L STOCKBRIDGE
01/07/2010



IND 104,390

**SPECIAL PROTOCOL ASSESSMENT –
NO AGREEMENT**

Catherine Bernard, Ph.D.
U.S. Agent for Pierre Fabre Dermatologie
10626 Wagon Box Way
Highlands Ranch, Colorado 80130

Dear Dr. Bernard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for propranolol oral solution.

We also refer to your August 18, 2009, request, received on August 19, 2009, for a special protocol assessment of a clinical protocol. The protocol is titled “A randomized, controlled, multidose, multicentre, 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).”

We have completed our review and, based on the information submitted, have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission.

We have the following responses to your comments/rebuttals that you based on the concerns we raised in our advice letter dated August 4, 2009.

Clinical Pharmacology and Pharmacometrics

1. We note that you plan to conduct a pharmacokinetic study in infants in parallel with the adaptive phase II/III study (V00400 SB 201). While we understand that following our advice to conduct the pharmacokinetic study prior to the phase II/III clinical study will delay your development program, our recommendation remains the same. Knowing the pharmacokinetics in infants will provide a sound scientific rationale for the dosage regimen (dose and interval) and pharmacokinetic analysis plan to use in your clinical trial and might ultimately be more efficient drug development. We do not, however, consider the later performance of a preliminary pharmacokinetic study as a “Hold” issue.

2. We have the following comments regarding the synopsis of the pharmacokinetic study in infants:
 - a. The characterization of pharmacokinetics should be based on a prospectively powered study to target a 95% CI within 60% and 140% of the point estimate for clearance and volume of distribution for propranolol in each age group.
 - b. The synopsis does not indicate whether the main metabolite 4-hydroxypropranolol will be quantified. Since it is pharmacologically active, we suggest you quantify the 4-hydroxy metabolite.
 - c. During the titration phase, first administration of the new dose will be carried out at the study site. This is an opportunity to collect plasma samples at lower doses to determine pharmacokinetic information at lower doses without the extra burden of an additional clinic visit. In other words, the pre-dose sample will provide steady-state trough measurement on the previous dose. Collecting such information will make it more feasible for you to conduct useful population pharmacokinetic analysis as suggested under the Statistical Methodology of the Synopsis.
 - d. The propranolol doses should be administered at specific, set time intervals (e.g., every 12 hours, but we realize that children's sleeping patterns may preclude exact dosing schedules).
3. The dosage regimens that you cite for the various indications range from bid to qid. Although we agree that a bid regimen is cited for some indications, every 8 hours, every 6 to 12 hours, every 6 hours, tid and qid regimens are also cited. The unpublished pilot trial in 32 infants with severe IH used "2 or 3 divided doses". However, you have *only* selected a bid regimen to test in your clinical trial. Given that the pharmacokinetics profile is also unknown in infants, you have not provided scientific justification that a bid regimen is the best dose to study in your clinical trial.

Statistics

4. Please refer to our response to Q6, below.
5. Please refer to our response to Q6, below.
6. In your protocol, we noted that you proposed to use z-tests to obtain the p-values for data in both stages and the weighted inverse normal combination function to come up with the final critical value. Nevertheless, the primary endpoint in your current protocol is a binary variable. If you still plan to use a categorical variable to assess the drug's efficacy, it would be more efficient to use a method better suited for a categorical variable, such as Cochran-Mantel-Haenszel (CMH) statistic or Logistic regression to analyze the data.

We also have a concern about the validity of your estimated treatment effect for your sample-size planning. Without support from historical data, it is unclear whether 20% to 35% difference in success rate between individual regimens and placebo would be appropriate; we suggest that you collect historical evidence and justify the effect size used for planning the sample size. We also suggest that you run a set of difficult to

assess hemangiomas to assess the inter-subject variability in the measurement of the lesions. Based on the study's ability to handle large variances you may decide to exclude some types of IH lesions.

You should note that when your primary endpoint is changed, the sample size justification needs to be modified accordingly.

7. A statement regarding the sample size reassessment is still included in Section 13.6.2 of protocol. Please make suitable changes.
8. For confirmatory trials, the adaptive algorithms cannot be left completely to IDMC. You need to prespecify the criteria for benefit vs. for risk to define the benefit/risk ratio for selecting the "best" regimen of propranolol. It is also not clear how you will select the final dose regimens based on both benefit/risk ratio and also the statistical test. Please clarify.
9. You need to pre-specify how alpha will be allocated to the secondary endpoints.
10. No remaining issues.
11. No remaining issues.

Clinical

12. Two well-controlled clinical studies showing efficacy and safety will be required for approval of propranolol for IH at the proposed p-value. A single study with a much more robust p-value (<0.01) may be sufficient to allow approval based on a single trial. The study of propranolol for IH is for a non-life threatening, subjective, symptomatic benefit. It is therefore reasonable to request either replicate results in the same or similar populations or an extremely convincing effect in a single study. The current study is not powered to yield convincing results.

We suggest that if you are concerned that once a positive result in your proposed study is made public you will have difficulty in enrolling additional patients, several strategies to assure a second study can help. The first is to initiate the second study at the same time you have decided on what doses to take into the last part of the adaptive design study. A second alternative is to enroll patients with hemangiomas that are not facial but whose cosmetic outcome can be balanced against whatever adverse event profile you have already determined.

The benefit of any treatment for an hemangioma would be defined by:

- The complete resolution of the hemangioma or at least the rapid decrease in size to minimize any consequence of mass effects of these hemangiomas.
- The speed at which the hemangioma is resolved.
- The residual scarring, if any, after final healing.

The study which you propose does not seem to address adequately these important outcomes.

13. We still recommend that the primary endpoint be a comparison to baseline (not the proposed pair-wise comparison) and suggest you use an Area Under the Curve (AUC) measurement of the IH.

The categorical comparison, that is, improvement or worsening leads to some unreasonable conclusions. For example, take two children who both start out with a lesion diameter of 3 cm. At week 12, the first child has a rapid decrease in the size of the hemangioma to 1.5 cm diameter; the second child has a modest decrease in size to 2.7 cm diameter. At week 16 the first child has an increase in size from 1.5 to 1.8 cm; the second child has no change in lesion size. The final measurement has again a small decrease in both. The first child has shrinkage from 1.8 to 1.6 cm lesion. The second child has a decrease from 2.7 to 2.5 cm. Even though the first child's lesion at the end of the observation period is smaller than that of the second child, the first child would be considered a failure (increase in 10% of lesion size at second measured visit); the second child would be considered a success.

Another alternative would be not to pair the assessment. Rather assess the IH at each point in time independently of the IH at any other point in time. We strongly recommend against using a categorical assessment of the IH.

14. We are still concerned that the investigator assessing the IH will not be sufficiently blinded to the age of the child based on the photography protocol. All assessments of efficacy related to lesion size should, furthermore, be blinded to the individual who is treating the subject. Methods to maintain this fire-wall should be described in your study.
15. We suggest that you define the criteria for measurement of the IH and strongly encourage you to perform a pilot study to determine that you have a precise method of measuring the IH. Patients with some IH may have to be precluded from your study since it is entirely unclear how one would measure some of the IH. For example a subject with a subcutaneous hemangioma of the lip or nose, the specific measurements of the size of the lesion at baseline and on therapy may be so difficult to standardize since not all the lesion is visible. You may decide to exclude subjects whose measurements are difficult. This exclusion should be prespecified.

You may also need to prespecify how measurements would be accomplished if there are more than one hemangiomas present. In addition, you would need to specify how measurements of central clearing of a lesion would alter the measurement of that lesion.

We disagree with your choice to not have additional centralized assessments at D7, D14, D21, W5 and W8. Rather, you will have the photos available post-study if a reassessment of the investigators' evaluations is considered pertinent. We still

recommend *centralized* assessments of the IH earlier than 12 weeks, in particular at weeks 3 or 4 and week 8. Since the decision to use propranolol on some lesions would depend on the ability of this treatment to rapidly shrink these lesions, these early assessments are imperative.

16. Please explain why you chose 24 weeks as the final assessment of efficacy. It would seem that you will not capture a full or substantial resolution of the IH by this time. We would recommend that the final time point be at when you anticipate at least 50% (but preferably 100%) of the lesion to have resolved. The other measurements should be appropriately spaced based on this time span.

The definition of treatment success should only include size. It is still unclear if color will be used in your categorical assessment of “stable, improved, success” since you plan on having available color photographs of the IH. Since the change in color does not alter the mass effect of the hemangioma. Color change seems irrelevant to the decision as to whether the change in the lesion size is beneficial.

We still recommend that a change much greater than 10% be used for defining success in the measurement of the IH (e.g., time to 50% reduction in IH AUC).

There needs to be an algorithm for the assessment of long-term scarring. Please include this in your protocol.

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104390	ORIG-1	PIERRE FABRE DERMATOLOGIE	PROPRANOLOL HCL ORAL SOLUTION

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/s/

NORMAN L STOCKBRIDGE
10/02/2009

**Meeting Minutes
November 10, 2009**

Drug: propranolol hydrochloride oral solution
Sponsor: Pierre Fabre Dermatologie
Application: IND 104,390
Proposed indication: proliferating infantile hemangiomas requiring systemic therapy
Date Request Ltr: October 6, 2009
Date Confirmation Sent: October 15, 2009
Meeting Type: Type A: Post-SPA "no agreement" follow-up meeting
Purpose: To address issues raised by The Agency in the SPA "no agreement" letter
Meeting Date: November 10, 2009
Meeting Time: 2 p.m. EST
Location: White Oak Building 22 Room 1415

THE AGENCY Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer, DCRP
Nhi Beasley, Pharm.D.	Medical Officer, DCRP
Dan Brum, PharmD, RAC	Regulatory Project Manager, DCRP
Jim Hung, Ph.D.	Director, Division of Biometrics I
Yeh-Fong Chen Ph.D.	Statistician, DB I
Hari Cheryl Sachs, M.D.	Team Leader, Medical Officer, Pediatric & Maternal Health Staff
Elizabeth Durmowicz, M.D.	Medical Officer, PMHS
Denise Pica-Branco, Ph.D.	Regulatory Project Manager, PMHS

Sponsor Participants:

Pierre Fabre Dermatologie

Pascal Lefrançois, PhD, Pierre Fabre Dermatologie CEO
Christine Chaumont, PhD, Project Director
Jean Jacques Voisard, MD, Head of Development

(b) (4)



External experts

(b) (4)



Catherine Bernard, PhD, US Regulatory Agent, International Regulatory Affairs Services Inc.

Background:

Pierre Fabre Dermatologie is developing propranolol hydrochloride oral solution for the treatment of proliferating infantile hemangiomas requiring systemic therapy. Several systemic treatments are currently employed in clinical practice including corticosteroids, vincristine, propranolol hydrochloride, interferon, etc.; however, none has been approved. The sponsor received orphan designation for the above indication on September 5, 2008.

Regulatory History

- January 31, 2009: Parallel Scientific Advice Meeting with sponsor and EMEA
- July 1, 2009: new IND submitted
- August 19, 2009: clinical Special Protocol Assessment (SPA) submitted
- October 2, 2009: SPA *no agreement* letter sent to sponsor
- October 8, 2009: Sponsor requested Type A follow-up meeting
- November 10, 2009: FDA internal meeting held 30 minutes prior to meeting with sponsor (no premeeting responses were sent to sponsor in advance of the face-to-face meeting)

Meeting Discussion Points

Note: Question numbers below correspond to those posed in original SPA

Questions 4, 5 and 6 (Statistics)

The Agency said they had no major concerns with the proposed statistical plans described in the sponsor's briefing package received October 28, 2009.

Question 7 (Sample Size Reassessment)

With regard to including a contingency plan to perform a sample size reassessment, FDA believed it might be useful to include it in the protocol if the expected treatment effect turns out to be smaller than the sponsor expected.

Question 8 (Interim Analysis)

In the briefing document, the sponsor states: "The second 'best' regimen will only be chosen for further study along with the 'best' regimen if the first stage of the study suggest that recruitment in the second stage will be compromised by a 1:1 randomization ratio." The sponsor believes studying more than one dose after the interim analysis will facilitate patient recruitment because a lower percentage of patients would be randomized to placebo. Regardless of this point, the Agency encouraged the sponsor to study more than one dose (as a means to gain dose-response information), that such plans should be prespecified, and that the primary focus will be distinguishing treatment from placebo in any number of different ways (i.e., testing only the highest dose, pooling doses, demonstrating a dose-response relationship, etc.). The sponsor is planning to enroll 35 patients per arm in the first stage and to enroll 70 patients per arm for additional exploratory analyses. The sponsor explained that dose exploration will be a secondary goal of the study. Dr. Hung reminded the sponsor that interim data can have lots of uncertainty, and that one should be very careful when using interim data to make inferences and decisions. The sponsor further assured the Agency that they will not stop the trial based on the interim analysis. With regard to safety, the Agency said they did not have any major concerns based on a recent query of the Adverse Event and Reporting System (AERS) database. The sponsor has not come across any reports of serious adverse events either.

Question 9 (Secondary Endpoints)

The Agency recommended that the sponsor choose secondary endpoints that are not essentially variations of the primary endpoint but rather endpoints that could lead to clinically relevant, independent claims (i.e., decreased need for an invasive procedure), assuming the study could be adequately powered. If the sponsor performs just a single trial, the Agency noted that the low p-value used for the primary endpoint ought to be used for each secondary endpoint as well. The sponsor had proposed two secondary endpoints, namely a) complete resolution at one year and b) residual scarring. The Agency agreed these endpoints were reasonable, and reminded the sponsor to control for the overall type I error rate and to analyze the endpoints in the order of highest likelihood of success.

Regarding choice of statistical methodology, the sponsor planned to use the serial gate keeping procedure in combination with the Hochberg procedures. They agreed to provide the Agency with additional information and noted that they are now in a process of writing a paper with their proposed method. They will share it with the Agency in the near future. Dr. Hung suggested the sponsor look into a newly developed method by Bretz et al that might be useful.

The sponsor is planning to break the blind at 24 weeks when they analyze the primary endpoint; the Agency cautioned the sponsor that evaluation of secondary endpoints could be influenced by knowledge of treatment group. The sponsor acknowledged the Agency's concern and will describe precisely how they will maintain the firewall between the 24-week analysis and the ongoing investigation in the SAP.

The Agency agreed that the primary endpoint "near complete resolution" of the lesions is acceptable.

Question 12, 13, 15, 16 (Endpoints, Statistical Analysis, Etc.)

- In terms of rating lesion severity, the sponsor explained that inter-rater variability appeared to be extremely low.
- The sponsor expects that approximately 10% of patients will drop out of the study, but they plan to follow all patients including dropouts. The Agency asked the sponsor to include such information in the SAP. The study will begin enrolling in January 2010 and the sponsor will submit the SAP at that time as well.
- The sponsor said the incidence of infantile hemangiomas in Blacks was very low.
- Regarding secondary endpoints, the sponsor had planned to ask investigators to categorize lesions as mild, moderate or severe during the open-label part of the study. The Agency felt these categories were subjective and would not lead to useful information unless perhaps the investigators were provided clear definitions of what constitutes degree of improvement.
- The Agency reiterated that several earlier measurements (i.e., prior to 24 weeks) be performed in a similar manner to the primary endpoint as a means to describe lesion resolution as a function of time.
- The sponsor plans to focus on facial lesions although lesions on other parts of the body will also be examined in exploratory analyses.
- The sponsor said that patients will be stratified as described in the protocol (e.g., age, gender); however, stratifying by baseline lesion severity would not be feasible.

IND 104,390 (propranolol hydrochloride oral solution)

Meeting Minutes

Page 4 of 4

November 10, 2009

Minutes preparation: *{See appended electronic signature page}*
Dan Brum, PharmD, MBA, RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, MD, PhD

Drafted (db): 11/11/09 Finalized (db): 11/16/09

Reviewed by:

Beasley: 11/11/09

Chen: 11/12/09

Hung: 11/12/09

Durmowicz: 11/12/09

Sachs: 11/13/09

Stockbridge: 11/13/09

Karkowsky: 11/13/09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104390	GI-1	PIERRE FABRE DERMATOLOGIE	PROPRANOLOL HCL ORAL SOLUTION

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/s/

DANIEL BRUM
11/16/2009

NORMAN L STOCKBRIDGE
11/16/2009