

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205410Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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|                              |   |
|------------------------------|---|
| <b>NDA Number</b>            | 205410                                  |
| <b>Submission Type; Code</b> | Original, N_00                          |
| <b>Applicant Name</b>        | Pierre Fabre Dermatologie               |
| <b>Submission Dates</b>      | 05/17/2013, 06/21/2013                  |
| <b>Brand Name</b>            | (b) (4)                                 |
| <b>Generic Name</b>          | Propranolol hydrochloride               |
| <b>Dosage Form</b>           | Solution for oral administration        |
| <b>Dosage Strengths</b>      | 4.28 mg/mL of propranolol hydrochloride |
| <b>Proposed Indication</b>   | Infantile hemangioma                    |
| <b>OCP Division</b>          | Division of Clinical Pharmacology 1     |
| <b>Primary Reviewer</b>      | Divya Menon-Andersen                    |
| <b>Team Leaders</b>          | Jeffry Florian, Rajanikanth Madabushi   |

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## 1 EXECUTIVE SUMMARY

Pierre Farbe Dermatologie is seeking approval of propranolol hydrochloride oral solution 4.28 mg/mL for use in the treatment of proliferating infantile hemangioma in this 505(b)(2) submission. Propranolol is a non-selective beta adrenergic receptor blocker that is approved for use in adults for several indications including the treatment of hypertension, angina, and heart failure. There are no approved treatments for infantile hemangioma.

In support of the indication the applicant conducted a 12 week pharmacokinetic study and a 24 week Phase 2/3 adaptive design study in infants with hemangioma. A relative bioavailability study was also conducted to establish a bridge to the reference listed drug, Inderal. The primary endpoint in the Phase 2/3 adaptive design study was complete or near complete resolution of the hemangioma at week 24. Propranolol showed a statistically significant increase in the proportion of patients achieving complete or near complete resolution as compared to placebo.

The to-be-marketed formulation was used in the phase 2/3 study.

### 1.1 Recommendations

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

### 1.2 Phase 4 Commitments

None.

### 1.3 Summary of Important Clinical Pharmacology Findings

The key findings are listed below.

1. Peak propranolol plasma concentrations were observed within 1 to 2 h of administration of the solution. Mean CL/F of propranolol was estimated to ~ 23 L/h. After accounting for body weight, propranolol pharmacokinetics in infants (mean ( $\pm$ SD) = 3.3 ( $\pm$ 1.7) L/h/Kg) is similar to that observed in adults (mean ( $\pm$ SD) = 3.8 ( $\pm$ 1.3) L/h/Kg).
2. Probability of complete/near complete resolution at week 24 appears to be dose dependent. The highest dose evaluated (3 mg/Kg/day) is close to maximal effect and a further increase in the dose is unlikely to result in a significant increase in response.
3. Of the propranolol treatment groups, > 50% of the patients in the 6 month duration arms achieved complete/near complete resolution while only ~ 5 to 10 % of the patients randomized to the 3 month arms achieved complete/near complete resolution indicating that continued treatment for at least 6 months is needed for resolution of the hemangioma.
4. There was no significant effect of propranolol treatment on blood pressure, heart rate, or blood glucose levels in infants.

## 2 QUESTION BASED REVIEW

### 2.1 General Attributes of the Drug

Propranolol is a non-selective beta adrenergic blocker first approved in 1967 (NDA 16418) for use in adults. The drug is approved for use in treatment of hypertension, angina, myocardial infarction, essential tremor, pheochromocytoma, and migraine. The starting dose ranges from 10 to 80 mg depending on the indication. The development program for propranolol oral solution was conducted under IND 104,390.

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Propranolol, 2-propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride, ( $\pm$ ), is a white crystalline solid readily soluble in water and ethanol.

Propranolol oral solution is formulated in a single strength of 3.75 mg/mL expressed as propranolol base equivalent to 4.28 mg/mL propranolol hydrochloride. The solution contains hydroxyethylcellulose, saccharin sodium, strawberry flavor, vanilla flavor, citric acid monohydrate and water as excipients.

The solution is packaged in a 120 mL bottle and is supplied with syringe adaptor and 5 mL oral syringe.

#### 2.1.2 What are the proposed mechanism of action and therapeutic indications?

Propranolol is hypothesized to affect infantile hemangioma via three mechanisms (1) vasoconstriction (2) inhibition of angiogenesis (3) induction of apoptosis.

Proliferating infantile hemangioma is characterized by endothelial cell proliferation. The lesion usually not detectable at birth, appears during the first 4 to 6 weeks of life and grows rapidly. The proliferative phase lasts until 6 to 12 months of age followed by stabilization of the lesion for the next 13 to 36 months of life. Spontaneous involution of the lesion occurs eventually by the age of 3 to 7 years<sup>1</sup>.

#### 2.1.3 What are the proposed dosages and routes of administration?

Propranolol oral solution will be marketed in a single strength of 3.75 mg/mL (expressed as propranolol base) for oral administration twice daily.

### 2.2 General Clinical Pharmacology

#### 2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

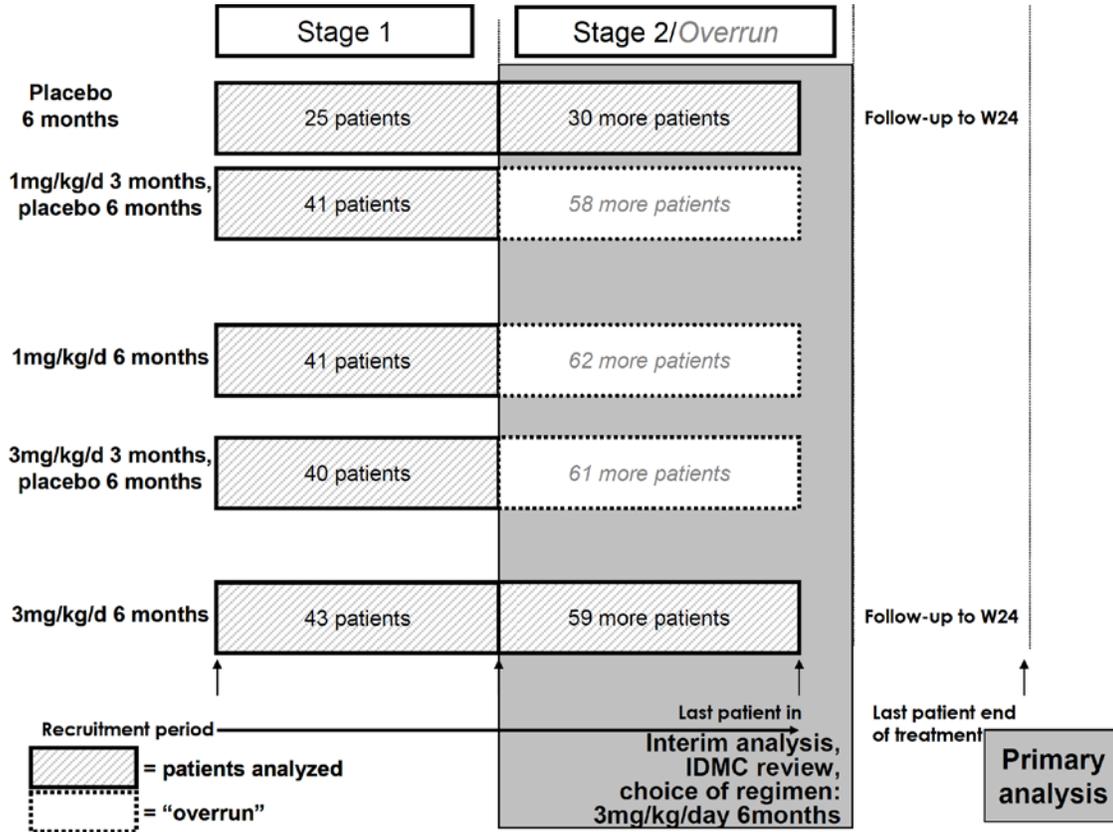
The submission consisted of three studies, a 12 week PK/PD study in 35 to 150 day old infants with hemangioma (V00400SB102), a relative bioavailability study conducted in

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<sup>1</sup> Leaute-labrezeet al, NEJM, 2008, 358(24):2649-51

healthy adults (V00400SB1012A), and an adaptive design Phase2/3 study (V0400SB201).

This Phase 2/3 study<sup>2</sup> in 35 to 150 day old infants with proliferating hemangioma and an open label follow up study were submitted in support of efficacy and safety. Four treatment regimens (1 or 3 mg/Kg/day for a duration of 3 or 6 months) of propranolol were compared against placebo in this study. A schematic of the study, as conducted, is presented in **Figure 1**.



**Figure 1** Schematic of the adaptive design Phase 2/3 study (Ref CSR V0400SB201).

### 2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Complete /near complete resolution of the target hemangioma at end of study (week 24) was the primary response endpoint in the efficacy study. Resolution of the hemangioma was assessed using photographs acquired following standardized procedure. Image color, size calibration, subject lighting and background, patient position, and angle and distance between the camera and patient were the parameters that were standardized.

<sup>2</sup> An interim analysis was conducted after 40 patients in each of the propranolol treated arms and 20 patients in the placebo treated arm of the study had completed 24 weeks (or been prematurely withdrawn) to recommend one or two treatment regimens to carry forward into the Phase 3 segment of the study. The IDMC recommended taking the 3 mg/Kg/day dose for duration of 6 months into Phase 3. However, in the interim a sufficient number of patients had been recruited in all treatment arms and the study was completed as such.

The photographs were read by two centralized readers. Quantitative assessments of the lesion (size and color) were conducted as secondary endpoints in the efficacy study.

### **2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

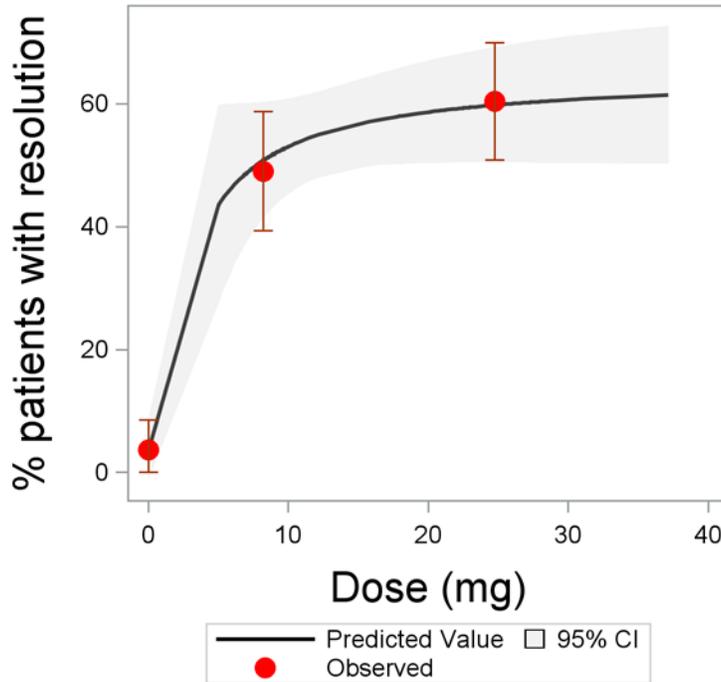
Propranolol and its 4-hydroxy metabolite were appropriately identified and measured in plasma to permit adequate assessment of pharmacokinetics.

## **2.2.4 Exposure-Response**

### **2.2.4.1 What are the characteristics of the dose-response relationships for efficacy?**

The probability of complete/near complete resolution at week 24 was dose-dependent based on an analysis of absolute dose administered in the Phase 2/3 study (see **Figure 2**). While the study evaluated three separate dose levels (placebo, 1mg/Kg/day, and 3 mg/Kg/day) the regression analysis shown in **Figure 2** was based on the total dose administered to each subject so as to get a wider range of dose to facilitate the analysis. Additional details summarizing the methodology and total dose range within treatment arms can be found below in the caption of **Figure 2**.

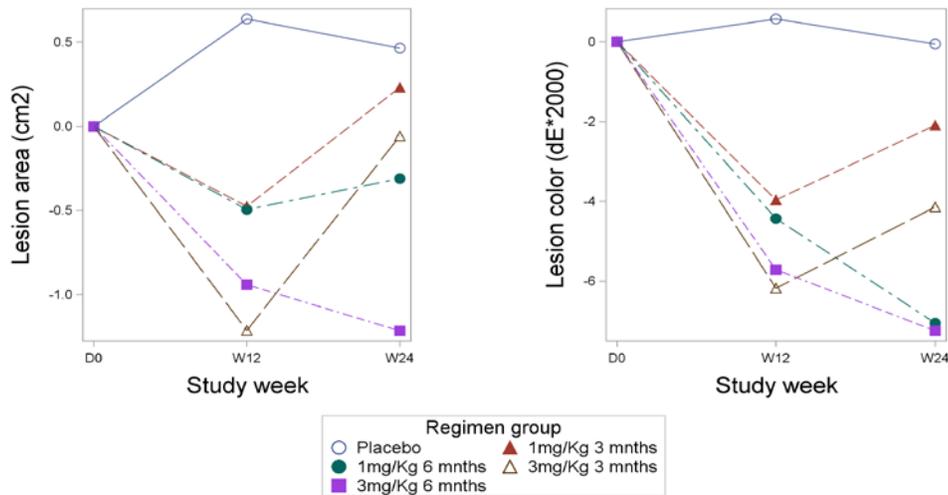
The dose-effect relationship increases steeply between placebo and lowest dose group, showing an improvement at both dose levels compared to placebo. A three-fold increase in dose, going from 1 to 3 mg/Kg, resulted in a 10% increase in probability of achieving lesion resolution. The highest dose evaluated (3 mg/Kg/day) appears to achieve maximal effect and a further increase in the dose is not predicted to significantly increase the probability of complete/near complete resolution.



**Figure 2** Probability of complete/near complete resolution (1° endpoint) at week 24 is dose dependent.

Total dose and probability of resolution of infantile hemangioma was modeled using logistic regression as a non-linear function using an  $E_{max}$  model. The solid line and shaded region represent the predicted probability and 95% confidence limits, respectively. The filled circles represent the observed proportion (95% confidence limits) of patients with resolution binned by treatment group (ie., placebo, 1 mg/Kg or 3 mg/Kg). The median (range) absolute dose for the 1 and 3 mg/Kg dose groups were 8.2 (5-12.2) mg and 24.8 (15.7-37.1) mg, respectively (VS00400SB201).

A trend towards a larger response with the higher dose was also observed in lesion color and size (quantitative measures collected as 2° endpoints) at week 12 (see **Figure 3**). As seen in **Figure 3**, the 3 mg/kg/day dose resulted in a numerically larger effect on lesion size at both weeks 12 and 24. In the case of lesion color, a dose dependent effect was observed at week 12 but not at week 24. One explanation for the lack of dose-response at week 24 is that, lesion color is measured as a contrast between the coloring of the lesion and the surrounding skin. As the lesion improves, there may be a diminished (floor effect) impact on this assessment. Additionally, the results indicate that treatment duration of 3 months is not sufficient to achieve complete resolution.



**Figure 3** Numerically higher magnitude of change from baseline in lesion size and color observed at higher dose.

#### 2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

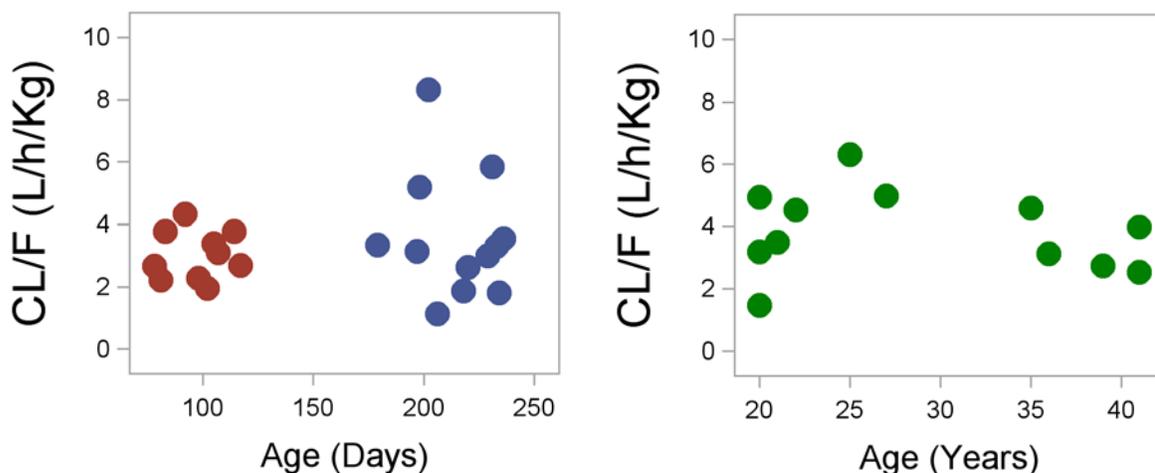
A trend towards lowering blood pressure, heart rate and blood glucose was observed in the Phase 2/3 study. However, this was neither dose dependent nor statistically significant. Maximal decrease for these measures was generally observed following administration of the first dose (1 mg/Kg).

#### 2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

The proposed dose of 3 mg/Kg *bid* (starting at 1 mg/Kg *bid* and titrated to 3 mg/Kg *bid* at weekly intervals in 1 mg/Kg/day increments) for a duration of at least 6 months is consistent with the observed safety profile and the exposure-response relationship for efficacy.

##### *Body weight based dosing*

Bodyweight based dosing, as proposed, provided similar propranolol exposure across the age group most likely to present with IH. As shown in **Figure 4** propranolol apparent clearance (CL/F), normalized to total body weight, was similar in infants < 90 days of age (at enrolment), > 90 days of age (at enrolment), and to that seen in adults (**V00400SB1012A**) indicating that a 'mg/Kg' dosing strategy will result in reasonably similar systemic exposure to propranolol across the age continuum.



**Figure 4** Propranolol apparent clearance (CL/F), when normalized to total body weight, is similar across age groups.

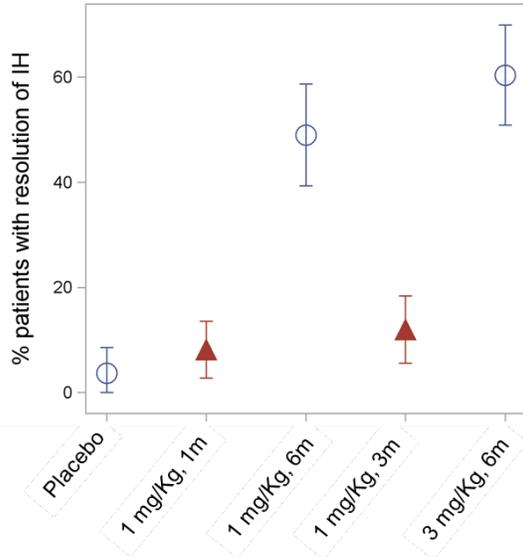
Six serial samples were collected at weeks 4 and 12 for pharmacokinetic assessments in study **V00400SB102**. Clearance was assessed using NCA and population PK methods. Estimates from both methods are in agreement. Propranolol clearance in adults was assessed using the data collected in the relative BA study (**V00400SB1012A**) for the oral solution. Age at PK sampling (weeks 4 and 12 of the study in infants) was used in the plots.

*Dose, dosing interval*

As previously discussed (see **Figure 2**) a numerically higher proportion of patients achieved complete/near complete resolution of the hemangioma at the higher dose of 3 mg/Kg when compared to the lower dose of 1 mg/Kg. Additionally, given the absence of a dose dependent effect on blood pressure or hypoglycemia (safety measures) titration to the higher dose of 3 mg/Kg is justified. Up-titration to the target dose (as is the case with beta blockers) at weekly intervals enables the cardiovascular system to adjust and also allows adequate monitoring for potential bradycardia and hypotension. Only a *bid* dosing regimen was evaluated in this development program. This is the lowest dosing frequency at which propranolol is dosed in adults. This dosing interval is also utilized in treating infantile hemangioma as reported in the literature.

*Duration of treatment*

The proportion of patients achieving complete/near complete resolution at week 24 (end of study) is presented in **Figure 5**. Of the propranolol treatment groups, > 50% of the patients in the 6 month duration arms achieved complete/near complete resolution while only ~ 5 to 10 % of the patients randomized to the 3 month arms achieved complete/near complete resolution indicating that continued treatment for at least 6 months is needed for resolution of the hemangioma.



**Figure 5** Proportion (mean and 95% CI) of patients with complete/near complete resolution in all treatment groups at week 24 in the Phase 2/3 study.

Open circles represent treatment groups of 6 month duration and the closed triangles represent treatment groups of 3 month duration.

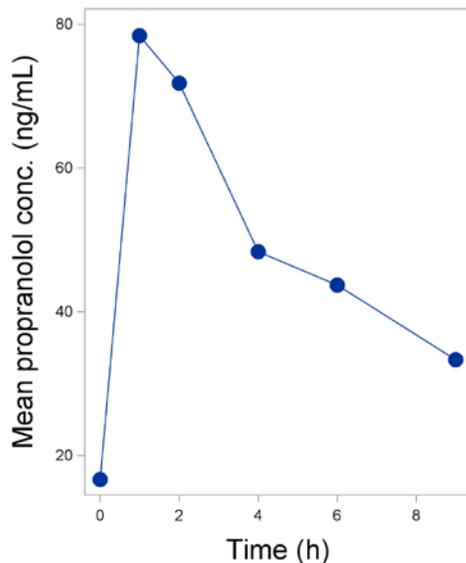
The results of the quantitative analysis of lesion size and color (see **Figure 3**) further support the choice of 6 month treatment duration.

## 2.2.5 What are the PK characteristics of the drug?

### 2.2.5.1 What are the single and multiple dose PK parameters?

Multiple dose pharmacokinetics of propranolol and its 4-hydroxy metabolite were evaluated following administration of 3 mg/Kg given *bid* in infants with proliferating hemangioma (V00400SB102).

Peak propranolol plasma concentrations were observed within 1 to 2 h of administration of the solution (see **Figure 6**). Mean CL/F of propranolol was estimated to ~ 23 (13) L/h in infants 35 to 150 days of age. The median (range) terminal elimination half-life ( $t_{1/2 \lambda}$ ) of propranolol was 3.5 (1.5-25.6) h.



**Figure 6** Mean steady state propranolol concentration versus time plot following administration of 3 mg/Kg propranolol as an oral solution in infants 35 to 150 days of age.

Peak 4-hydroxy propranolol plasma concentrations were also observed within 1 to 2 h of administration of the solution. Total systemic exposure ( $AUC_{0-9h}$ ) to the metabolite was ~ 5% that of propranolol and is similar to that reported in adults<sup>3</sup>.

#### **2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients (infants)?**

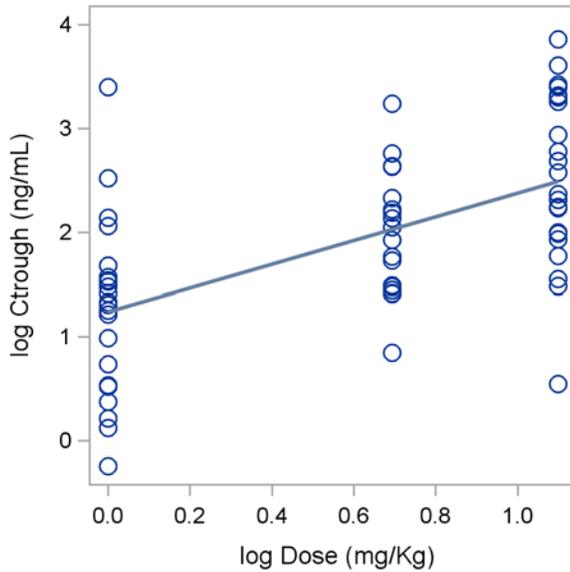
The clearance of propranolol in infants (mean ( $\pm$ SD) = 3.3 ( $\pm$ 1.7) L/h/Kg) is similar to that observed in adults (mean ( $\pm$ SD) = 3.8 ( $\pm$ 1.3) L/h/Kg). Please see section 2.2.4.3.

#### **2.2.5.3 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?**

The pharmacokinetics of propranolol is dose proportional in the dose range of 1 to 3 mg/Kg/day in infants. The power model fit is presented in **Figure 7** ( $\beta \rightarrow 1.13$  (SE 0.2)).

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<sup>3</sup> Christer et al, Br.J.Clin.Pharmacol, 1982, 14:79-82



**Figure 7** Propranolol pharmacokinetics is dose proportional.

Pre-dose samples were collected for pharmacokinetic assessment prior to dose up-titration on days 7 and 14 in study **V00400SB102**.

### 2.3 General Biopharmaceutics

#### 2.3.1 Was the relative bioavailability study conducted to serve as a bridging study adequate?

The relative bioavailability study conducted to provide a context for interpreting the pre-clinical data associated with the reference listed drug Inderal® is adequate. Mean systemic exposure (AUC and C<sub>max</sub>) to propranolol following administration of the oral solution is ~ 20% higher than Avlocardyl® (propranolol hydrochloride tablet marketed in Europe). The study was conducted in 12 healthy adults and was not designed to establish bioequivalence. *In vitro* dissolution data for Avlocardyl® and Inderal® were then compared to complete the bridge (reviewed by ONDQA biopharm).

#### 2.4 Analytical Section

The bioanalytical method used to support the PK study satisfied all criteria for ‘method validation’ and ‘application to routine analysis’ set by the ‘Guidance for Industry: Bioanalytical Method Development’, and was therefore acceptable (see **Table 1**).

**Table 1:** Assay validation results for propranolol and 4-OH propranolol (report # FAB/PRO/09003).

|                          | <b>Propranolol</b>  | <b>4-OH propranolol</b>  |
|--------------------------|---|--|
| Standard curve range     | 0.5 to 250 ng/mL<br>(weighted 1/x <sup>2</sup> , r > 0.99)                          | 0.5 to 250 ng/mL<br>(weighted 1/x <sup>2</sup> , r > 0.99)                     |
| QC sample concentrations | 0.5, 1.5, 125, 200 ng/mL  | 0.5, 1.5, 125, 200 ng/mL   |
| Precision (%CV)          | Intra-run: ± 9.4 %<br>At LLOQ: ± 10.2 %<br>Inter-run: ± 11.3 %<br>At LLOQ: ± 10.6 % | Intra-run: ± 7.8%<br>At LLOQ: ± 13.5%<br>Inter-run: ± 6.7 %<br>At LLOQ: ± 10 % |
| Accuracy (bias)          | Intra-run: - 6 %<br>At LLOQ: - 12 %   | Inter-day: -6.0%<br>At LLOQ: -4.0 %  |

|                    |   |   |
|--------------------|---|---|
|                    | Inter-run: -0.9 %<br>At LLOQ: -6 %  | Inter-day: -4 %<br>At LLOQ: 0 %   |
| Internal standard  | D7 – propranolol (racemate)<br>Lot number: R499P62  | 4-OH prop – D7<br>Lot number: F231BP22/F231BP26   |
| Reference standard | Propranolol (racemate)<br>Lot number: 8083PRRII<br>Purity: 100.1%   | 4-hydroxypropranolol<br>Lot number: AL-3890<br>Purity: 98%  |
| Specificity        | No interference   | No interference   |
| Recovery           | Propranolol: 84.1%<br>D7 – propranolol: 84.7 %  | 4-OH prop: 85.8%<br>4-OH prop – D7: 86.8%   |
| Matrix             | Human plasma, lithium heparinized   | Human plasma, lithium heparinized   |
| Stability          | Benchtop: 4 hours<br>4°C: 31 days<br>Freeze-thaw: 3 FT cycles<br>Long term at -20°C: 182 days<br>Long term at -80°C: 182 days | Benchtop: 6 hours<br>4°C: 21 days<br>Freeze-thaw: 3 FT cycles<br>Long term at -20°C: 100 days<br>Long term at -80°C: 182 days |

### 3 APPENDICES

#### 3.1 Individual Study Reviews

##### 3.1.1 Study V00400 SB 102 (Pharmacokinetics and Pharmacodynamics)

|  |  |             |                      |                 |            |         |        |                |      |
|--|--|-------------|----------------------|-----------------|------------|---------|--------|----------------|------|
| <b>Study Protocol #</b> V00400 SB 102  | <b>Study period</b> 05/28/2010 to 06/07/2011 |             |                      |                 |            |         |        |                |      |
| <p><b>Title</b></p> <p>A multicenter, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile hemangiomas (IH) requiring systemic therapy <sup>4</sup>.</p>   |  |             |                      |                 |            |         |        |                |      |
| <p><b>Objectives</b></p> <p>The primary objective was to assess pharmacokinetics of propranolol in infants following administration as a solution.</p>   |  |             |                      |                 |            |         |        |                |      |
| <p><b>Study Design</b> This was a 12 week, open-label, multicenter, repeat dosing study conducted in infants 35 to 150 days of age. A total of 23 infants, grouped by age (Group 1, n=10 → 35 to 90 days; Group 2, n=13 → 91 to 150 days) with any type of proliferating hemangioma were enrolled in the study. The dose was up-titrated at weekly intervals in increments of 1 mg/Kg/day given <i>bid</i> to reach the target dose of 3 mg/Kg/day given <i>bid</i>. Study medication was administered in the morning and in the late afternoon (1700 h) to avoid possible occurrences of hypoglycemia going unnoticed by the parents. Parents were instructed to administer the evening dose at 2000 h before the PK sampling visit (visit 4 and 12). There were five scheduled visits (at weeks 1, 2, 4, 8, 12) during the study and a follow up visit 2 weeks after the study was completed. At each visit the dose was re-calculated by the investigator.</p> <p>Note: The age range in this study represent the proliferating phase of the disease. Citing a study by Chang et al, the applicant notes that most IH growth before 5 months and 80% of the full hemangioma was reached at a mean age of month 3. The duration of study was based on what was reported to be effective in literature.</p> |  |             |                      |                 |            |         |        |                |      |
| <p><b>Study medication</b></p> <table border="1" data-bbox="284 1470 1128 1625"> <tr> <td>Dosage Form</td> <td>Propranolol solution</td> </tr> <tr> <td>Dosage Strength</td> <td>3.75 mg/mL</td> </tr> <tr> <td>Batch #</td> <td>SB0753</td> </tr> <tr> <td>Administration</td> <td>Oral</td> </tr> </table>   |  | Dosage Form | Propranolol solution | Dosage Strength | 3.75 mg/mL | Batch # | SB0753 | Administration | Oral |
| Dosage Form  | Propranolol solution                         |             |                      |                 |            |         |        |                |      |
| Dosage Strength  | 3.75 mg/mL                                   |             |                      |                 |            |         |        |                |      |
| Batch #  | SB0753                                       |             |                      |                 |            |         |        |                |      |
| Administration   | Oral   |             |                      |                 |            |         |        |                |      |
| <p><b>Study assessments</b></p> <p>Pharmacokinetic: Blood samples (250 µL) were collected at pre-dose on days 7 and 14 of the study and at pre-dose, 1, 2, 4, 6, and 9 h post dosing on day 28 for infants in group 1</p>  |  |             |                      |                 |            |         |        |                |      |

<sup>4</sup> \\cdsesub1\evsprod\nda205410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\v00400-sb-102\clinical-study-report.pdf

and day 84 for infants in group 2 of the study.

Pharmacodynamic: Blood pressure, heart rate and blood glucose were measured at pre-dose, 1, 2, 3, and 4 hours post dose up-titration on days 7 and 14, and at pre-dose at subsequent visits.

Qualitative assessment of (1) change in the target hemangioma was performed using a three point scale - improvement, stabilization, worsening (in comparison to previous visit) (2) complete or near complete resolution. The target IH complications were also graded at each visit.

**Data Analysis Methods**

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV). Pharmacodynamic data were summarized as means (SD).

**Study population**

|  |                |
|--|----------------|
| Enrolled/Completed/ Discontinued because of AE | 23/23/0        |
| Mean age (range) in days                       | 102.7 (50-152) |
| 35 to 90 days                                  | 69.7 (50-89)   |
| 91 to 150 days                                 | 128.2 (91-152) |
| Male/Female                                    | 17/6           |
| Race   | Not recorded   |
| Weight in Kg                                   | 5.64 (4.3)     |
| 35 to 90 days                                  | 4.76 (0.7)     |
| 91 to 150 days                                 | 6.32 (1.0)     |

*Please also see 'Detailed results' section.*

**Results:**

- Total (AUC<sub>0-9h</sub>) and peak (C<sub>max</sub>) systemic exposure to propranolol and its 4 hydroxy metabolite were similar in infants 35 to 90 days of age and 91 to 150 days of age.
- The mean elimination half-life of propranolol was 5 and 8 h, in infants 35 to 90 days of age and 91 to 150 days of age, respectively.
- The increase in propranolol trough concentration was approximately dose proportional in both age groups.
- Maximal decrease from baseline in blood pressure was observed following administration of the first dose of 1 mg/Kg (Gp 1 → mean (SD) SBP - 8.7 (9.6) mm Hg, mean (SD) DBP -7 (7) mm Hg; Gp 2 → mean (SD) SBP - 5.6 (13.5) mm Hg, mean (SD) DBP -5 (15.4) mm Hg). Subsequent dose escalation on days 7 and 14 did not result in further drops in blood pressure. The observations were highly variable and do not show a consistent decrease/change over time.
- Maximal decrease from baseline in blood glucose was observed following administration of the first dose of 1 mg/Kg (Gp 1 → mean (SD) 7.3 (34.3) mg/dL, Gp 2 → mean (SD) 6.3 (11.4) mg/dL). Subsequent dose escalation on days 7 and 14 did not result in further drops in blood pressure. The observations were highly variable and do

not show a consistent decrease/change over time.

**Assay Method**

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

|                 |                         |                         |
|-----------------|-------------------------|-------------------------|
| Analyte         | Propranolol             | 4-OH-propranolol        |
| Method          | LC/MS/MS                | LC/MS/MS                |
| LOQ (ng/mL)     | 0.5                     | 0.5                     |
| Range (ng/mL)   | 0.5 to 250              | 0.5 to 250              |
| QCs (ng/mL)     | 1.5, 12.5, 50, 125, 200 | 1.5, 12.5, 50, 125, 200 |
| Accuracy (bias) | -6 to 0.7%              | -7 to 0.7%              |
| Precision       | ± 7%                    | ± 5.4%                  |

**Safety** Death/SAE: None

**Conclusion**

The pharmacokinetics, pharmacodynamics and tolerability of propranolol in infants 35 to 150 days of age were characterized.

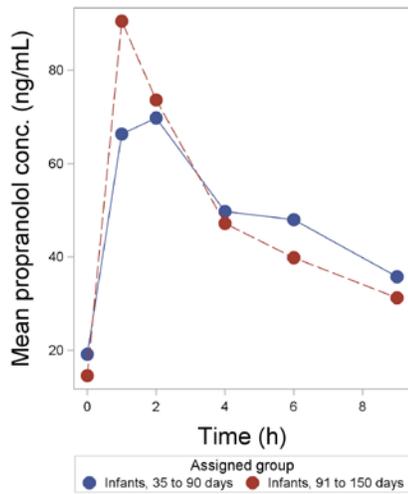
**Detailed Results:**

**Table** Summary of pharmacokinetic measures/parameters for propranolol and 4-OH propranolol following oral administration (Ref: CSR V00400 SB 102)

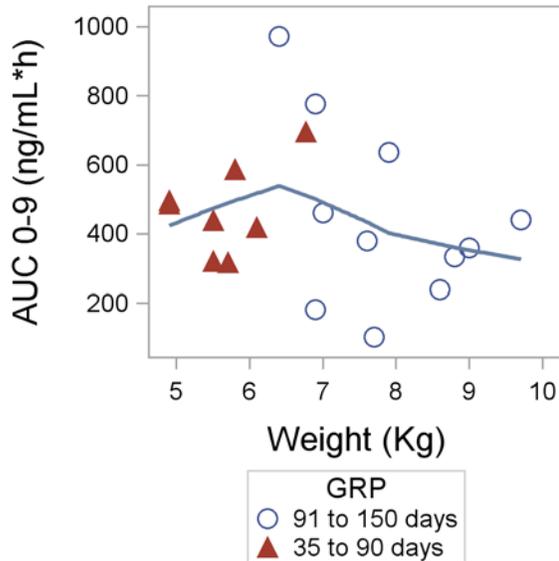
| Group   | Propranolol / Mean (%CV) |               | 4-OH propranolol / Mean (%CV) |           |
|---|--------------------------|---------------|-------------------------------|-----------|
|   | I                        | II            | I                             | II        |
| AUC <sub>0-9h</sub><br>(ng/mL*h)                    | 455 (28)                 | 373 (72)      | 27.4 (42)                     | 16.2 (55) |
| C <sub>max</sub> (ng/mL)                            | 78.5 (33)                | 79.2 (103)    | 6.2 (53)                      | 3.8 (88)  |
| T <sub>max</sub> (h)                                | 2 (1 - 9)                | 2 (1 - 4)     | 1.1 (1 - 2)                   | 2 (1 - 4) |
| CL/F (L/h)  | 15.2 (28)                | 25.5 (79)     | -                             | -         |
| t <sub>1/2</sub> (h)*                               | 3.5 (2.1-25.6)           | 3.6 (1.5-6.2) | -                             | -         |
| *Median(range), CSR V00400 SB 102 Appendix 16.2.5.3 |                          |               |                               |           |

**Pharmacokinetics**

*Concentration - time course*



**Figure** Mean propranolol concentration versus time plot following administration of 3 mg/Kg propranolol in infants < 90 days (●) and infants 90 to 150 days (●).

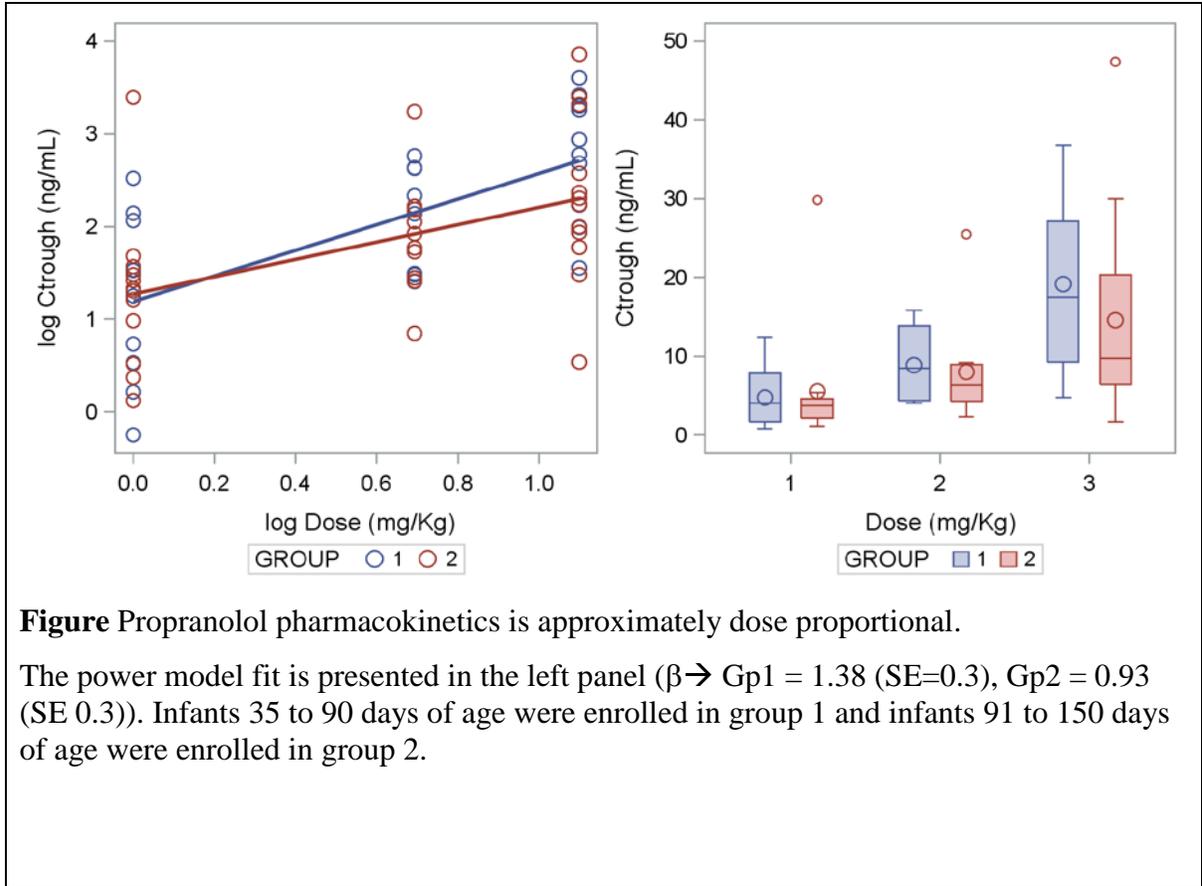


**Figure** Total body weight based dosing provides similar propranolol plasma concentrations in infants 35 to 150 days of age.

The symbols represent the individual observations of  $AUC_{0-9h}$  and the solid line represents the loess fit and serves to show trends in the data.

Note: (1) Weight presented on the x-axis corresponds to the infant's weight on the PK sampling day (day 28 for < 90 day old infants and day 84 for > 90 day old infants).

(2) Age and weight are correlated in this population and a plot of age (days) vs. AUC



**Figure** Propranolol pharmacokinetics is approximately dose proportional.

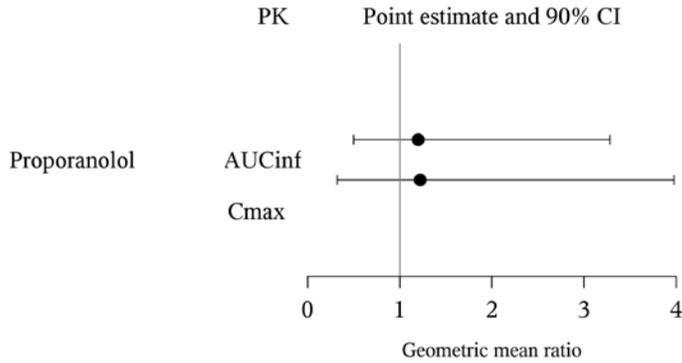
The power model fit is presented in the left panel ( $\beta \rightarrow Gp1 = 1.38$  (SE=0.3),  $Gp2 = 0.93$  (SE 0.3)). Infants 35 to 90 days of age were enrolled in group 1 and infants 91 to 150 days of age were enrolled in group 2.

### 3.1.2 Study VS00400SB1012A (Relative bioavailability)

|  |              |  |  |
|--|--------------|--|--|
| <b>Study Protocol #</b> VS00400SB1012A   |              | <b>Study period</b> 06/22/2009 to 07/20/2009 |  |
| <b>Title</b><br>Evaluation of pharmacokinetic parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol formulation (tablet). A single centre, randomized open-label, two-way crossover study <sup>5</sup> .                                   |              |  |  |
| <b>Objectives</b><br>To assess systemic exposure to propranolol following administration of (b) (4) compared to that following administration of Avlocardyl® in the fasted state.  |              |  |  |
| <b>Study Design</b><br>Open label, randomized, two period, crossover study, with a minimum of three days of washout between study periods.   |              |  |  |
| <b>Study medication</b>  |              |  |  |
| Dosage Form  | Tablet 70 mg | Solution 5 mg/mL                             |  |
| Batch #  | 84013        | CLP080                                       |  |
| Administration   | oral         |  |  |
| <b>Sampling schedule</b><br>Blood samples were collected for pharmacokinetic analysis at pre-dose, 0.3, 0.6, 1, 1.3, 1.6, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose.   |              |  |  |
| <b>Data Analysis Methods</b><br>Summary statistics were calculated and presented for PK measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed. |              |  |  |
| <b>Study population</b>  |              |  |  |
| Randomized/Completed/ Discontinued Due to AE   |              | 12/12/0                                      |  |
| Age (range) years  |              | 29 (20-41)                                   |  |
| Male/Female  |              | 12/12  |  |
| Race (Caucasian/Black/Asian/American Indian or Alaska native/other)  |              | 12/0/0/0/0                                   |  |

<sup>5</sup> \\cdsub1\evsprod\nda205410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\v00400-sb-101-2a\clinical-study-report.pdf

**Results:**



**Figure** Bioavailability of propranolol following administration of the oral solution (b) (4) compared to the tablet (Avlocardyl®). The closed circles represent the geometric mean and the horizontal line represents the 90% CI associated with the mean.

**Assay Method**

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

|                   |               |
|-------------------|---------------|
| Analyte           | Propranolol   |
| Method            | HPLC/MS/MS    |
| LOQ (ng/mL)       | 0.5           |
| Range (ng/mL)     | 0.5 to 250    |
| QCs (ng/mL)       | 1.5, 125, 200 |
| Accuracy/Bias (%) | 98-103 %      |
| Precision (%CV)   | ± 5%          |

**Safety** Death/SAE: None

**Conclusion**

Mean total and peak systemic exposure to propranolol was ~ 20% higher following administration of the solution as compared to the tablet.

**Detailed Results:**

**Table** Summary of pharmacokinetic measures/parameters for propranolol following oral administration.

|                          | Propranolol mean (% CV or range) |            |
|--------------------------|----------------------------------|------------|
|                          | tablet                           | solution   |
| Dosage form              | tablet                           | solution   |
| AUC (ng/mL*h)            | 314.8 (92)                       | 328.2 (39) |
| C <sub>max</sub> (ng/mL) | 52.8 (95)                        | 49.5 (27)  |
| T <sub>max</sub> (h)     | 1.7 (0.7-3)                      | 1.3 (1-2)  |
| t <sub>1/2</sub> (h)     | 4.2 (15)                         | 4.4 (14)   |
| CL/F (L/h)               | 372.5 (58)                       | 269.6 (30) |
| L/h/Kg                   | 5.3 (58)                         | 3.8 (34)   |

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/s/  
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DIVYA MENON ANDERSEN  
01/17/2014

JEFFRY FLORIAN  
01/18/2014

RAJANIKANTH MADABUSHI  
01/18/2014

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

|                                 |   |  |         |
|---------------------------------|---|--|---------|
| <b>Application No.:</b>         | NDA 205-410   | <b>Reviewer:</b> Kareen Riviere, Ph.D.             |         |
| <b>Submission Date:</b>         | 5/17/13   |  |         |
| <b>Division:</b>                | DCRP  | <b>Team Leader:</b> Angelica Dorantes, Ph.D.       |         |
| <b>Applicant:</b>               | Pierre Fabre Dermatologie   | <b>Acting Supervisor:</b> Richard Lostritto, Ph.D. |         |
| <b>Trade Name:</b>              | (b) (4)   | <b>Date Assigned:</b>                              | 5/21/13 |
| <b>Generic Name:</b>            | Propranolol oral solution   | <b>Date of Review:</b>                             | 1/7/14  |
| <b>Indication:</b>              | Treatment of proliferating infantile hemangioma (IH) requiring systemic therapy | <b>Type of Submission:</b> 505(b)(2) NDA           |         |
| <b>Formulation/strengths:</b>   | Oral Solution/ 3.75 mg/mL   |  |         |
| <b>Route of Administration:</b> | Oral  |  |         |

**SUMMARY:**

This submission is a 505(b)(2) New Drug Application for (b) (4) (propranolol) Oral Solution, 3.75 mg/mL. The proposed indication is for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy.

The clinical development for the product was based on three clinical trials: two Phase 1 studies (one in healthy adults and one in infants with hemangioma) and one pivotal Phase 2/3 efficacy and safety study in infants with proliferating IH requiring systemic therapy. There is pharmacokinetic, efficacy, and safety data/information on the to-be marketed formulation. However, the non-clinical program relies on NDA 16-418 for Inderal® (propranolol hydrochloride), which is the listed drug that is the basis for this submission.

The Applicant's approach for the bridging of the proposed product and the reference listed drug (RLD), Inderal® tablets is as follows:

1. An *in vivo* bioavailability comparison between the proposed product and a French approved propranolol tablet formulation (Avlocardyl®, the French brand name for Inderal®).
2. An *in vitro* dissolution study comparing the dissolution profiles of Avlocardyl® 40 mg tablets and Propranolol HCl USP 40 mg tablets approved under ANDA 71-974.

The focus of this Biopharmaceutics review is the evaluation and acceptability of the information/data supporting the bridging between the proposed propranolol product and the RLD propranolol product under NDA 16-418. Note that this bridging is needed to leverage propranolol's non-clinical information.

**RECOMMENDATION:**

ONDQA-Biopharmaceutics has evaluated the overall information/data and considers that the scientific evidence provided to bridge the proposed oral solution product to the listed drug, Inderal® 40 mg tablets is appropriate and acceptable based on the following:

- 1) Propranolol is reported to be a BCS-Class 1 drug. Therefore, it is a highly soluble and highly permeable drug substance. In addition, the overall dissolution data in house have shown that

Avlocardyl® 40 mg tablets, Propranolol HCl USP 40 mg tablets (ANDA 71974), and Inderal® tablets are fast dissolving immediate release tablets and therefore based on BCS, it is expected that these products would behave as solutions in vivo without any bioavailability issues.

- 2) Note that Avlocardyl® contains mannitol, an inactive ingredient known to affect (decrease) the bioavailability of drug products. However, the results from the provided BE study between the proposed propranolol oral solution product and Avlocardyl® 40 mg tablets showed that the two products are bioequivalent in vivo; demonstrating that the inclusion of mannitol in the formulation of this product does not have an effect on its bioavailability and therefore it can be assumed that the Inderal® tablet, which does not contain mannitol, will also be bioequivalent to the oral solution.
- 3) The data under ANDA 71-974 showed that the Propranolol HCl 40 mg USP tablets and the Inderal® 40 mg tablets are bioequivalent and that these products have similar dissolution profiles. Also, the data provided in this submission showed that Avlocardyl® 40 mg tablets and Propranolol HCl 40mg USP tablets have similar dissolution profiles. Therefore, as BCS-Class 1, highly soluble, highly permeable, fast dissolving drug products, it is expected that the Avlocardyl® 40 mg tablets and Inderal® 40 mg tablets would have not only similar dissolution profiles, but also similar in vivo performance.
- 4) In addition, there are in vivo pharmacokinetic data and data from a Phase 2/3 data on the commercial formulation of the proposed Propranolol Oral Solution product, which provides further evidence of the characterization of the pharmacokinetics, as well as the efficacy and safety of the proposed product.

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

**Kareen Riviere, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**

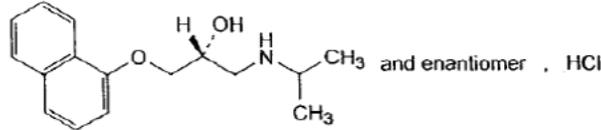
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

# ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

## 1. Background

Propranolol is reported as a BCS Class I (high solubility, high permeability) drug substance in the published literature (Takagi *et al.*, *Molecular Pharmaceutics* 2006). The chemical structure of propranolol is shown in Figure 1.



**Figure 1.** Chemical Structure of Propranolol

The composition of the formulation of the proposed propranolol oral solution drug product is shown in Table 1.

**Table 1.** Composition of the Drug Product

| Component   | Quantity per mL | Quantity per bottle (120 mL filled) | Function         | Reference to Quality Standard        |
|---|-----------------|-------------------------------------|------------------|--------------------------------------|
| <b>Drug substance</b>                                       |                 | (b) (4)                             |                  |                                      |
| Propranolol base  | 3.75 mg         |                                     | Active substance | USP                                  |
| (corresponding to propranolol hydrochloride) <sup>(1)</sup> | (4.28 mg)       |                                     |                  |                                      |
| <b>Excipients</b>   |                 |                                     |                  |                                      |
| Hydroxyethyl Cellulose (b) (4)                              |                 |                                     | (b) (4)          | USP/NF                               |
| Saccharin sodium  |                 |                                     |                  | USP                                  |
| Strawberry flavour (b) (4)                                  |                 |                                     |                  | In-house specification (MMP-17884-C) |
| Vanilla flavour (b) (4)                                     |                 |                                     |                  | In-house specification (MMP-18371-C) |
| Citric acid monohydrate                                     |                 |                                     |                  | USP                                  |
| Water, (b) (4)  |                 |                                     |                  | USP                                  |

The clinical development for the product was based on three clinical trials: two Phase 1 studies (one in healthy adults and one in infants with hemangioma) and one pivotal Phase 2/3 efficacy and safety study in infants with proliferating IH requiring systemic therapy.

Table 2 presents the qualitative and quantitative composition of the formulations used throughout the clinical development and the commercial formulation.

**Table 2. Formulations used in Clinical Trials and Commercial Formulation**

| Component                                  | Phase 1 PK clinical study (adults) | Phase 1 PK clinical study (children) | Phase 2/3 clinical study |                     |                     |                     | Commercial formulation |                     |
|--|------------------------------------|--------------------------------------|--------------------------|---------------------|---------------------|---------------------|------------------------|---------------------|
|  | 5 mg/mL solution                   | 3.75 mg/mL solution                  | 1.25 mg/mL solution      | 2.50 mg/mL solution | 3.75 mg/mL solution | 3.75 mg/mL solution | Placebo                | 3.75 mg/mL solution |
| <b>Drug substance</b>                      |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Propranolol base                           | 5.00 mg                            | 3.75 mg                              | 1.25 mg                  | 2.50 mg             | 3.75 mg             | 3.75 mg             |                        | 3.75 mg             |
| corresponding to Propranolol hydrochloride | 5.70 mg                            | 4.28 mg                              | 1.43 mg                  | 2.85 mg             | 4.28 mg             | 4.28 mg             |                        | 4.28 mg             |
| <b>Excipients</b>                          |                                    |                                      |                          |                     |                     |                     |                        | (b) (4)             |
| Hydroxyethyl cellulose (b) (4)             |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Saccharin sodium (b) (4)                   |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Strawberry flavour (b) (4)                 |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Vanilla flavour (b) (4)                    |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Vanilla flavour (b) (4)                    |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Citric acid monohydrate (b) (4) water      |                                    |                                      |                          |                     |                     |                     |                        |                     |
| Formula code                               |                                    |                                      |                          |                     |                     |                     |                        |                     |

The formulation of the propranolol oral solution tested in Phase 1 studies and Phase 2/3 studies is the same. This formulation is not significantly different from the proposed commercial formulation. Therefore, there is PK, efficacy, and safety supportive information/data on the proposed to-be marketed formulation.

**2. Bridging the Proposed Oral Solution Product to Inderal® 40 mg Tablets**

The listed drug that is the basis for this submission is Inderal® (propranolol hydrochloride) approved under NDA 16-418. However, a BE study between the proposed oral solution product and Inderal® tablets was not conducted and the Applicant proposes to bridge the proposed product and the listed drug using the following approach:

1. An *in vivo* bioavailability/bioequivalence study between the proposed product and a French approved propranolol tablet formulation (Avlocardyl®, the French brand name for Inderal®).
2. An *in vitro* dissolution study, which compared the dissolution profiles of Avlocardyl® 40 mg tablets and Propranolol HCl USP 40 mg tablets approved under ANDA 71-974 and manufactured by PLIVA and distributed by Barr, which is now a sub-division of Teva Pharmaceuticals.

In the May 9, 2012 meeting minutes for the pre-NDA meeting held with the Applicant on April 24, 2012, FDA stated the following ”

*”the proposed bridging program (described above) is an acceptable approach and the acceptability of the data will ultimately be a review issue”.*

**Reviewer’s Comment:**

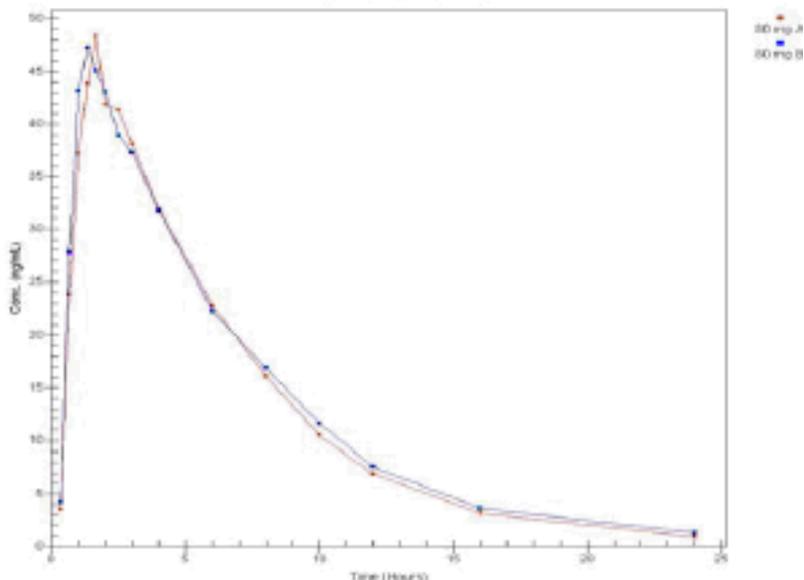
*Note that the Applicant proposed the above bridging approach because they claimed that the Inderal® 40 mg tablet was no longer marketed in the United States and therefore they could not use Inderal® as the reference listed drug in the BE study supporting the approval of their product. However, a search on Drugs@FDA shows that Inderal 40 mg is still being marketed in the U.S.*

➤ **Evaluation of In Vivo Data**

**Pharmacokinetic:** The results of the *in vivo* bioavailability/bioequivalence study (Study V00400 SB 1 01 2A) between the proposed propranolol Oral solution product and Avlocardyl®, a French approved propranolol tablet

formulation demonstrated in 12 healthy adults comparable bioavailability profiles between the 2 formulations, indicating that both products are bioequivalent. The mean plasma concentration profiles are shown in Figure 2.

**Figure 2.** Mean Propranolol Plasma Concentration-Time Curves after Administration of Propranolol as the Reference Tablet (A, 70.18 mg) and as the Solution (B, 80 mg)



**Note:** The Clinical Pharmacology Reviewer, Dr. Divya Menon-Andersen is currently evaluating the PK study and will provide a recommendation regarding its acceptability.

**Clinical:** The Applicant conducted a Phase 2/3 adaptive design study (No. V00400 SB201) to support the efficacy of the proposed drug product. The safety analysis comprises data from more than 2,451 patients treated with propranolol in the clinical trials (424 patients), CUP (660 patients) and literature review of scientific publications (1,367 patients with IH treated with propranolol). The safety and efficacy information was evaluated by the Medical Reviewer, Khin Maung U, M.D. and he is recommending approval, pending some labeling revisions.

➤ **Evaluating Compositional Similarity**

A qualitative formulation comparison of Avlocardyl® and Propranolol Hydrochloride USP tablets is shown in Table 3.

**Table 3.** Qualitative Composition of Avlocardyl® and Propranolol HCl USP tablet

| Trade mark                          | Active ingredient (dosage)      | Excipients  |
|-------------------------------------|---------------------------------|---|
| Avlocardyl®                         | Propranolol HCl<br>(40 mg/unit) | <ul style="list-style-type: none"> <li>- D manitol</li> <li>- Gelatine</li> <li>- Alginic acid</li> <li>- Stearic acid</li> <li>- Magnesium stearate</li> </ul>   |
| Propranolol HCl tablets USP (Barr)* | Propranolol HCl<br>(40 mg/unit) | <ul style="list-style-type: none"> <li>- Anhydrous lactose</li> <li>- Magnesium stearate</li> <li>- Crystalline micro cellulose</li> <li>- Sodium starch glycolate</li> <li>- FD and C yellow</li> <li>- FD and C blue</li> </ul> |

The labeling for Inderal® tablets indicates that the inactive ingredients contained in the tablet formulation are lactose, magnesium stearate, microcrystalline cellulose, stearic acid, and FD&C Blue No. 1.

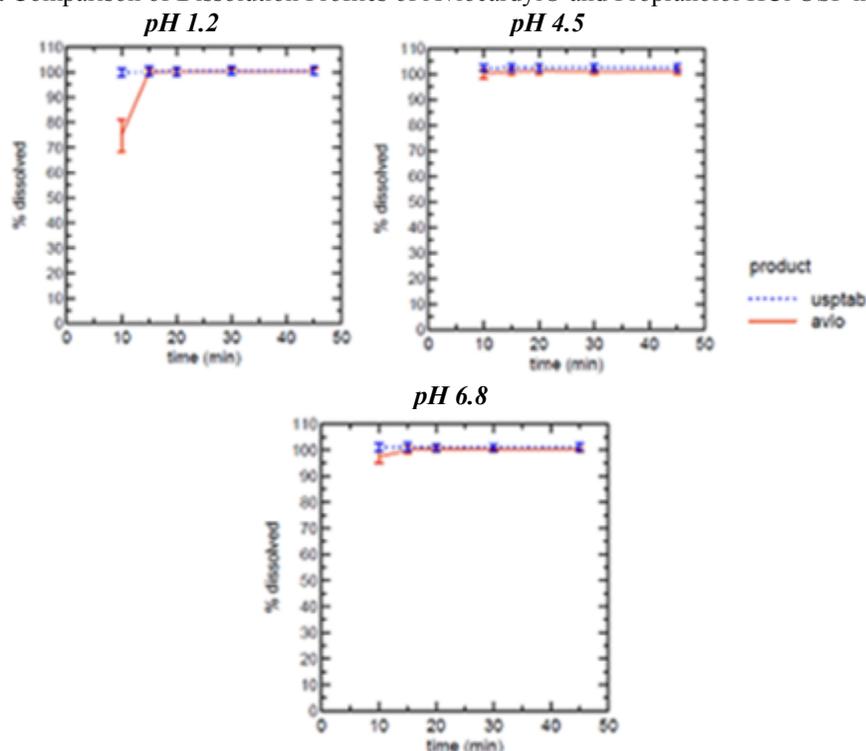
**Reviewer's Assessment:**

Table 3 shows that the composition of Avlocardyl® 40 mg tablet and Propranolol HCl USP 40 mg tablet are not quantitatively and qualitatively similar. The composition of Propranolol HCl USP 40 mg tablet is qualitatively similar to that of the Inderal® 40 mg tablet. Therefore, it can be concluded that Avlocardyl® 40 mg tablet and Inderal® 40 mg tablet are not quantitatively and qualitatively similar.

➤ **Evaluating Dissolution Similarity**

The Applicant compared the *in vitro* dissolution profiles of 40 mg Avlocardyl® and 40 mg Propranolol Hydrochloride USP tablets in pH 1.2, 4.5, and 6.8 buffers using Apparatus 1 at 100 rpm agitation speed (refer to Figure 3a,b,c).

**Figure 3 a, b, c.** Comparison of Dissolution Profiles of Avlocardyl® and Propranolol HCl USP in Different Media



**Reviewer's Assessment:**

The data in Figure 3 a, b, c show that more than  $\frac{(b)}{(4)}$  % of the label amount of propranolol HCl in both drug products is dissolved within 15 minutes in mild dissolution test conditions. This result is expected since these products contain a BCS-Class 1 drug substance in a rapidly dissolving tablet formulation. Since Avlocardyl® and Propranolol HCl USP have similar dissolution profiles, they are anticipated to have similar *in vivo* performance.

The 40 mg Propranolol HCl USP tablets (ANDA 71-974) have an AB rating on the Drugs@FDA website. According to the FDA Orange Book, multisource drug products listed under the same heading (i.e., identical active ingredient(s), dosage form, and route(s) of administration) and having the same strength generally will be coded AB if a study is submitted demonstrating bioequivalence. Therefore, these tablets already are demonstrated to be bioequivalent and to have similar dissolution profiles to Inderal® 40 mg tablets under ANDA 71-974.

Additionally, since propranolol is a BCS, Class 1 highly soluble/highly permeable drug substance and the 40 mg Avlocardyl® tablets and 40mg Propranolol HCl USP tablets are fast dissolving products with similar dissolution profiles and the 40 mg Propranolol HCl USP tablets and the Inderal® 40 mg tablets had shown to be bioequivalent, it is expected that 40 mg Avlocardyl® tablets and Inderal® 40 mg tablets would have similar dissolution profiles and also similar *in vivo* performance.

**Reviewer's Overall Assessment of the Bridging Data:**

*Under an optimal regulatory situation, the Applicant should have used in the conducted BE study, Inderal® 40mg tablets, which is the U.S. RLD product instead of Avlocardyl® 40mg tablets (French product). The Applicant's justified this change claiming that the Inderal® 40 mg tablets were not longer marketed in the U.S. However, this change is not fully justified because a search on Drugs@FDA shows that Inderal 40 mg tablets are still being marketed and are available in the U.S. Note that the Applicant is a French company and they used in the BE study the French propranolol listed product instead of the U.S. RLD product. It is possible that the Applicant did not have access to the U.S. RLD product.*

*Note that in general when Sponsors/Applicants propose to use an European listed drug product instead of the U.S. RLD product in a pivotal BE study, FDA can waive the need for an additional BE study comparing the proposed product to the U.S. RLD product, if the Applicant demonstrates that the EU RLD and the US RLD have the same qualitative and quantitative composition, were manufactured in a similar manner, and have similar dissolution profiles. Therefore, for the BE waiver the Applicant should have had provided a head-to-head comparison of the quantitative and qualitative composition as well as the manufacturing process for Inderal® and Avlocardyl®. Instead, they provided comparative information for Avlocardyl® and Propranolol HCl USP, a generic propranolol product. The information shows that composition of Avlocardyl® 40 mg tablet and Propranolol HCl USP 40 mg tablet are not quantitatively and qualitatively similar. The composition of Propranolol HCl USP 40 mg tablet is qualitatively similar to that of the Inderal® 40 mg tablet. Therefore, it can be concluded that the Avlocardyl® 40 mg tablet and Inderal® 40 mg tablet are NOT quantitatively and qualitatively similar.*

*Strictly from a regulatory perspective, A BE waiver is not appropriate for the proposed product due to the fact that Avlocardyl® 40 mg tablets and Inderal® 40 mg tablets and the proposed propranolol oral solution are different dosage forms and do NOT meet the requirement of "similar composition". However, FDA accepted the Applicant's bridging proposal because there is strong scientific evidence supporting the bioequivalence among these propranolol products. First, propranolol is a BCS Class 1 (high solubility and high permeability) drug substance. Second, the dissolution data showed that the products are fast dissolving. Fast dissolving immediate release drug products containing a BCS class I drug such as propranolol are expected to behave as a solution in vivo. Hence, it is expected that Avlocardyl®, Propranolol HCl USP, and Inderal® products behave as solutions in vivo, provided the formulation does not contain any inactive ingredients that may significantly alter the bioavailability of the active ingredient. Although Avlocardyl® contains mannitol, which may affect the bioavailability (decrease) of the drug product, the results from the BE study demonstrated that this product is bioequivalent to the oral solution; therefore, it can be assumed that the Inderal® tablet, which does not contain mannitol, will be bioequivalent to the oral solution as well.*

*Furthermore, the 40 mg Avlocardyl® tablets and 40mg Propranolol HCl USP tablets have similar dissolution profiles and 40 mg Propranolol HCl USP tablets and the Inderal® 40 mg tablets are bioequivalent. Therefore, it is expected that the 40 mg Avlocardyl® tablets and Inderal® 40 mg tablets would have similar dissolution profiles and have similar in vivo performance. Thus, there is a preponderance of evidence that indicates that the proposed oral solution product and the U.S. RLD are bioequivalent and that a BE waiver is adequate for this product.*

*In conclusion, the proposed oral solution product and the U.S. listed drug, Inderal® 40 mg tablets, are adequately bridged based on the following:*

- 1) Propranolol is a BCS class 1 drug substance. Therefore the 40 mg Avlocardyl®, Propranolol HCl USP, and Inderal® tablets are expected to act as solutions in vivo since they are formulated and manufactured to be fast dissolving immediate release tablets.*
- 2) Since Avlocardyl®, which contains mannitol, an inactive ingredient that may affect the bioavailability (decrease) of drug products, still is bioequivalent to the oral solution; it can be deduced that the Inderal® tablet, which does not contain mannitol, will also be bioequivalent to the oral solution.*
- 3) The 40 mg Avlocardyl® tablets and 40mg Propranolol HCl USP tablets have similar dissolution profiles and 40 mg Propranolol HCl USP tablets and the Inderal® 40 mg tablets are bioequivalent. Therefore, it is expected that the 40 mg Avlocardyl® tablets and Inderal® 40 mg tablets would have similar dissolution profiles and have similar in vivo performance.*
- 4) There is PK data and phase 2/3 data on the commercial formulation of the proposed product which provides further evidence of efficacy and safety of the proposed product.*

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KAREEN RIVIERE  
01/07/2014

ANGELICA DORANTES  
01/07/2014

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**  
*New Drug Application Filing and Review Form*

General Information About the Submission

(b) (4) (propranolol oral solution, 3.75 mg/mL) will be used in the treatment of proliferating infantile hemangioma. Its mechanism of action in this condition is not known. The development program was conducted under IND 104390.

|   | Information          |                         | Information                     |
|---|----------------------|-------------------------|---------------------------------|
| NDA/BLA Number  | 205410               | Brand Name              | (b) (4)                         |
| OCP Division (I, II, III, IV, V)                      | I                    | Generic Name            | Propranolol                     |
| Medical Division                                      | DCRP                 | Drug Class              | Beta blocker                    |
| OCP Reviewer  | Divya Menon-Andersen | Indication(s)           | Infantile hemangioma            |
| OCP Team Leader                                       | Raj Madabushi        | Dosage Form             | Solution                        |
| Pharmacometrics Reviewer<br>Pharmacogenomics Reviewer | -                    | Dosing Regimen          | Twice daily                     |
| Date of Submission                                    | 05/17/2013           | Route of Administration | Oral                            |
| Estimated Due Date of OCP Review                      | 10/17/2014           | Sponsor                 | Pierre Fabre<br>Pharmaceuticals |
| Medical Division Due Date                             |                      | Priority Classification | Standard                        |
| PDUFA Due Date  | 03/17/2014           |                         |                                 |

***Clin. Pharm. and Biopharm. Information***

|  | "X" if included at filing | Number of studies submitted | Number of studies reviewed (tentative) | Critical Comments If any           |
|--|---------------------------|-----------------------------|--|------------------------------------|
| STUDY TYPE   |                           |                             |  |                                    |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                         |                             |  |                                    |
| Tabular Listing of All Human Studies   | X                         |                             |  |                                    |
| HPK Summary  | X                         |                             |  |                                    |
| Labeling   | X                         |                             |  |                                    |
| Reference Bioanalytical and Analytical Methods                                 | X                         |                             |  |                                    |
| I. Clinical Pharmacology   |                           |                             |  |                                    |
| Mass balance:  |                           |                             |  |                                    |
| Isozyme characterization:  |                           |                             |  |                                    |
| Blood/plasma ratio:  |                           |                             |  |                                    |
| Plasma protein binding:  |                           |                             |  |                                    |
| Pharmacokinetics (e.g., Phase I) -   | X                         | 1                           | 1                                      | PK/PD study (Study # VS00400SB102) |
| Healthy Volunteers-  | X                         |                             |  |                                    |
| single dose:   |                           |                             |  |                                    |
| multiple dose:   |                           |                             |  |                                    |
| Patients-  |                           |                             |  |                                    |
| single dose:   |                           |                             |  |                                    |
| multiple dose:   | X                         | 1                           | 1                                      | PK/PD study (Study # VS00400SB102) |
| Dose proportionality -   |                           |                             |  |                                    |
| fasting / non-fasting single dose:   |                           |                             |  |                                    |
| fasting / non-fasting multiple dose:   |                           |                             |  |                                    |
| Drug-drug interaction studies -  |                           |                             |  |                                    |
| In-vivo effects on primary drug:   |                           |                             |  |                                    |
| In-vivo effects of primary drug:   |                           |                             |  |                                    |

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

|   |   |   |   |   |
|---|---|---|---|---|
| In-vitro:   |   |   |   |   |
| Subpopulation studies -                                       |   |   |   |   |
| ethnicity:  |   |   |   |   |
| gender:   |   |   |   |   |
| pediatrics:   |   |   |   |   |
| geriatrics:   |   |   |   |   |
| renal impairment:   |   |   |   |   |
| hepatic impairment:   |   |   |   |   |
| PD -  |   |   |   |   |
| Phase 2:  |   |   |   |   |
| Phase 3:  |   |   |   |   |
| PK/PD -   |   |   |   |   |
| Phase 1 and/or 2, proof of concept:                           | X | 1 | 1 | PK/PD study (Study # VS00400SB102)  |
| Phase 3 clinical trial:                                       |   |   |   |   |
| Population Analyses -   |   |   |   |   |
| Data rich:  | X | 1 | 1 | Data collected in Study # VS00400SB102<br>(mainly provides description of PK) |
| Data sparse:  |   |   |   |   |
| II. Biopharmaceutics  |   |   |   |   |
| Absolute bioavailability                                      |   |   |   |   |
| Relative bioavailability -                                    | X |   |   | Relative BA study with IR tablet as the<br>reference (Study # VS004SB101)     |
| solution as reference:  |   |   |   |   |
| alternate formulation as reference:                           | X | 1 | 1 |   |
| Bioequivalence studies -                                      |   |   |   |   |
| traditional design; single / multi dose:                      |   |   |   |   |
| replicate design; single / multi dose:                        |   |   |   |   |
| Food-drug interaction studies                                 |   |   |   |   |
| Bio-waiver request based on BCS                               |   |   |   |   |
| BCS class   |   |   |   |   |
| Dissolution study to evaluate alcohol induced<br>dose-dumping |   |   |   |   |
| III. Other CPB Studies  |   |   |   |   |
| Genotype/phenotype studies                                    |   |   |   |   |
| Chronopharmacokinetics  |   |   |   |   |
| Pediatric development plan                                    |   |   |   |   |
| Literature References   |   |   |   |   |
| Total Number of Studies                                       |   | 2 | 2 |   |

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NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

|   | Content Parameter  | Yes | No | N/A | Comment                           |
|---|--|-----|----|-----|-----------------------------------|
| <b>Criteria for Refusal to File (RTF)</b>   |  |     |    |     |                                   |
| 1   | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?   |     |    | √   |                                   |
| 2   | Has the applicant provided metabolism and drug-drug interaction information?   |     |    | √   | Previously evaluated and in label |
| 3   | Has the sponsor submitted bioavailability data satisfying the CFR requirements?  | √   |    |     |                                   |
| 4   | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?   | √   |    |     |                                   |
| 5   | Has a rationale for dose selection been submitted?   | √   |    |     |                                   |
| 6   | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?  | √   |    |     |                                   |
| 7   | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?   | √   |    |     |                                   |
| 8   | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?   | √   |    |     |                                   |
| <b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b> |  |     |    |     |                                   |
| <b>Data</b>   |  |     |    |     |                                   |
| 9   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?  | √   |    |     |                                   |
| 10  | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?  |     |    | √   |                                   |
| <b>Studies and Analyses</b>   |  |     |    |     |                                   |
| 11  | Is the appropriate pharmacokinetic information submitted?  | √   |    |     |                                   |
| 12  | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?                            | √   |    |     |                                   |
| 13  | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?   |     |    | √   |                                   |
| 14  | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? |     |    | √   |                                   |
| 15  | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?   |     |    | √   |                                   |
| 16  | Did the applicant submit all the pediatric exclusivity data, as described in the WR?   |     |    | √   |                                   |
| 17  | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?   | √   |    |     |                                   |
|   |  |     |    |     |                                   |

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

| <b>General</b> |   |   |  |   |  |
|----------------|---|---|--|---|--|
| 18             | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | √ |  |   |  |
| 19             | Was the translation (of study reports or other study information) from another language needed and provided in this submission?   |   |  | √ |  |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

|  |               |
|--|---------------|
| Divya Menon-Andersen                       | 06/19/2013    |
| _____<br>Reviewing Clinical Pharmacologist | _____<br>Date |
| Raj Madabushi                              | 06/19/2013    |
| _____<br>Team Leader/Supervisor            | _____<br>Date |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIVYA MENON ANDERSEN  
07/08/2013

RAJANIKANTH MADABUSHI  
07/08/2013

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

|   |   |
|---|---|
| <b>NDA Number</b>                               | 205-410   |
| <b>Submission Date</b>                          | 5/17/2013   |
| <b>Product name, generic name of the active</b> | (b) (4) (propranolol) Oral Solution   |
| <b>Dosage form and strength</b>                 | Oral Solution; 3.75 mg/mL   |
| <b>Applicant</b>                                | Pierre Fabre Dermatologie   |
| <b>Clinical Division</b>                        | DCRP  |
| <b>Indication</b>                               | Treatment of proliferating infantile hemangioma (IH) requiring systemic therapy |
| <b>Type of Submission</b>                       | 505(b)(2)   |
| <b>Biopharmaceutics Reviewer</b>                | Kareen Riviere, Ph.D.   |
| <b>Biopharmaceutics Team Leader</b>             | Angelica Dorantes, Ph.D.  |
| <b>Acting Biopharmaceutics Supervisor</b>       | Richard Lostritto, Ph.D.  |

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

| <b>ONDQA-BIOPHARMACEUTICS</b>                                       |  |            |           |  |
|---|--|------------|-----------|--|
| <b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b> |  |            |           |  |
|   | <b>Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b>   |
| 1.  | Does the application contain dissolution data?                                       | x          |           | See the Initial Assessment below.  |
| 2.  | Is the dissolution test part of the DP specifications?                               |            | x         | Not Applicable.  |
| 3.  | Does the application contain the dissolution method development report?              |            | x         | Not Applicable.  |
| 4.  | Is there a validation package for the analytical method and dissolution methodology? |            | x         | Not Applicable.  |
| 5.  | Does the application include a biowaiver request?                                    | x          |           | See the Initial Assessment below.  |
| 6.  | Is there information provided to support the biowaiver request?                      | x          |           | See the Initial Assessment below.  |
| 7.  | Does the application include an IVIVC model?   |            | x         | Not Applicable.  |
| 8.  | Is information such as BCS classification mentioned, and supportive data provided?   | x          |           | The Applicant reported that propranolol hydrochloride is BCS Class I (high solubility, high permeability) compound and provided a published article to support this claim.   |
| 9.  | Is information on mixing the product with foods or liquids included?                 | x          |           | To anticipate the case of infants for which the oral solution could not be directly delivered in the buccal cavity, the Applicant performed compatibility studies with the proposed drug product in the milk and in fruit juice. |

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

|     |   |   |  |   |
|-----|---|---|--|---|
| 10. | Is there any <i>in vivo</i> BA or BE information in the submission? | x |  | The Applicant conducted an <i>in vivo</i> bioavailability study comparing the proposed product and a French approved propranolol tablet formulation (Avlocardyl®). These data will be reviewed by the Clinical Pharmacology reviewer. |
|-----|---|---|--|---|

| B. FILING CONCLUSION |   |     |    |         |
|----------------------|---|-----|----|---------|
|                      | Parameter   | Yes | No | Comment |
| 11.                  | <b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>  | x   |    |         |
| 12.                  | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant. | -   | -  |         |
| 13.                  | Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?  |     | x  |         |

*{See appended electronic signature page}*

Kareen Riviere, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

07/03/2013  
Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

07/03/2013  
Date

# PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

## INITIAL ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

The Applicant developed a pediatric oral solution intended to be administered to infants for the treatment of proliferative IH requiring systemic therapy. The clinical development for the product was based on three clinical trials: two Phase 1 studies (one in healthy adults and one in infants with hemangioma) and one pivotal Phase 2/3 efficacy and safety study in infants with proliferating IH requiring systemic therapy. There is PK, efficacy, and safety data/information on the to-be marketed formulation.

The reference listed drug product that is the basis for this submission is Inderal® (propranolol hydrochloride), NDA 16-418. Since Inderal® 40 mg tablet is no longer marketed, the Applicant proposes to bridge the proposed product and the reference drug product using a 2-step approach:

1. An *in vivo* bioavailability comparison between the proposed product and a French approved propranolol tablet formulation (Avlocardyl®, the French brand name for Inderal®), which demonstrated in 12 healthy adults comparable bioavailability profiles between the 2 formulations.
2. An *in vitro* dissolution test which demonstrated the equivalence of dissolution profiles of Avlocardyl® and Propranolol HCl USP 40 mg tablets (Barr Laboratories, Inc.), as Inderal® 40 mg tablet is no longer marketed).

In the May 9, 2012 meeting minutes for the pre-NDA meeting held with the Applicant on April 24, 2012, FDA stated that the proposed two-step “bridging” program (described above) is an acceptable approach and that acceptability of the data will ultimately be a review issue.

The Biopharmaceutics information in this submission includes multipoint dissolution profile comparison in pH 1.2, 4.5, 6.8 and f2 testing between Avlocardyl® (the French brand name for propranolol hydrochloride) and the US RLD Propranolol HCl USP tablet.

The Biopharmaceutics review will focus on the evaluation and acceptability of the dissolution data to support the Applicant’s two-step bridging approach.

### **RECOMMENDATION:**

The ONDQA Biopharmaceutics team has reviewed NDA 204031 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

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/s/  
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KAREEN RIVIERE  
07/03/2013

ANGELICA DORANTES  
07/05/2013