BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 20-839/Supplement S-051 IND 34,663 (Clopidogrel Bisulfate)	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	July 15, 2010	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DCRP	**Date of Review:**	January 11, 2011
Sponsor:	sanofi-aventis U.S. Inc.		
Trade Name:	Clopidogrel Bisulfate	**Type of Submission:** (b) (4) Supplement (b) S-051 (Pediatric Exclusivity Request)	
Generic Name:	Plavix		
Indication:	Plavix is a P2Y12 platelet inhibitor indicated for: • Acute coronary syndrome • Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.		
Formulation/strength	Tablets/ 75 mg		
Route of Administration	Oral		
Type of Review:	**Evaluation of the pediatric formulation used in the CLARINET pivotal trial**		

SUBMISSION:

Plavix® (clopidogrel bisulfate) Tablets were approved by the Agency under NDA 20-839 on November, 17 1997. Plavix is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. In NDA 20-839/ (b) (4) S-051, sanofi-aventis is seeking the approval of additional six months exclusivity for Plavix® Tablets based on the data submitted in response to the pediatric written request. Data from the three following studies were provided in the (b) (4) S-051 submission:

- A bioavailability study (BDR4580) comparing a liquid formulation suitable for pediatric administration to a 75 mg Plavix® tablet
- A dose-ranging study (PICOLO) to determine the dose of clopidogrel achieving 30% to 50% inhibition of 5 µM ADP-induced platelet aggregation in neonates and infants/toddlers at risk for thrombosis.
- A placebo-controlled, double-blind efficacy study (CLARINET) of 0.2 mg/kg clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary shunt.

The results of the CLARINET clinical study failed to show a statistically significant difference in the frequency of the primary efficacy endpoint of death, stent thrombosis, or cardiac procedure prior to 120 days considered as thrombotic in nature (20.5% for placebo, vs. 19.1% for 0.2 mg/kg/day clopidogrel bisulfate).

BIOPHARMACEUTICS:

The purpose of the Biopharmaceutics review is to evaluate the data supporting the acceptability of the pediatric formulation of clopidogrel bisulfate used in the pivotal clinical trial CLARINET and provide a recommendation.

Plavix Formulation: The formulation of the commercial Plavix 75 mg Tablets is presented in the following Table.

PLAVIX (Clopidogrel Bisulfate) TABLET FORMULATIONS

(b) (4)

[redacted]

Pediatric Formulations: The development history and overview of the clinical formulation used in the pivotal pediatric clinical trial, CLARINET are provided in the next summary tables containing all the formulation changes performed during the development of this pediatric formulation.

Pediatric Formulations - History of Formulation Changes

Clopidogrel Bisulfate - Active Powder		
Development Phase	**Dosage strength (expressed as base)**	**Formulation changes**

(b) (4)

[redacted]

Solvent for oral solution		
Development Phase	**Deliverable volume**	**Formulation changes**
(b) (4)		

For the Phase 3 study intended for up to 1 year of treatment in neonates and infants, a (b) (4) multi-dose palatable constituted oral solution was developed. (b) (4) .

Overview - Pediatric Formulation Development

	PHASE 1	PHASE 2	PHASE 3
Treatment Duration	**Single dose - Adults**	**7 to 28 days - Children**	**Up to 1 year - Children**
(b) (4)			

BIOAVAILABILITY Information:

The next table describes the composition of the three formulations used in the BA and pediatric studies.

Formulations Used in the Clopidogrel Pediatric Studies

	BDR4580 BA Study	PDY4422 PICOLO Trial	EFC-5314 CLARINET Trial
Form	(b) (4)		
Final concentratio			
Constituted pH			
Buffer			
Solubilizer			
Flow enhancer			
Bioavailability Studies	**Yes** (Solution vs. Plavix tablet in adults)	**No**	**No**

BA Study: Study BDR4580 conducted in 2002, evaluated the relative bioavailability between the commercial clopidogrel formulation (Plavix® tablets, 75 mg) and the 75 mg solution of Clopidogrel (SR25990C) following single oral administration to young healthy men. The results from the BA study showed that the pediatric-solution formulation and Plavix® tablets commercial formulation were not bioequivalent with respect to Cmax of the inactive clopidogrel metabolite. The rate of absorption of the inactive metabolite of clopidogrel was higher when the drug was administered as solution when compared with the tablet, resulting in a 15% higher mean Cmax (90% CI 1.02, 1.30) and a shorter Tmax. The compared treatments were bioequivalent in terms of extent of absorption (AUCs) of inactive clopidogrel metabolite.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the biopharmaceutic information supporting the pediatric-solution formulation of clopidogrel used in the pivotal clinical trial CLARINET provided in NDA 20-839/ (b) (4) S-051 for Plavix® Tablets and has the following comments:

Reviewer Comments:

1. ***It should be noted that at the time the BA study was conducted (2002) the assay for the active metabolite was not available. However, currently it is feasible to measure the parent compound and the active metabolite. Therefore, if we were to evaluate this BA study to currents standards, it would not be acceptable.***

2. ***Although, the pediatric formulation used in the CLARINET trial is a solution, it includes*** (b) (4) (b) (4) ***is an inactive ingredient that has an effect on the small intestine transit (SIT) time and influences the bioavailability of the formulations, independently if they are solid dosage forms (tablets/capsules) or solutions. Increasing the rate of SIT reduces the time available for drug absorption and may contribute to impaired absorption of luminal contents. Therefore, the incorporation of an excipient like*** (b) (4) ***into a pharmaceutical formulation would lead to reduced bioavailability.***

3. ***Additionally, there are other factors that may had affected the bioavailability of the formulation used in the CLARINET trial such as; 1) the lack of*** (b) (4) ***in the formulation, 2) the precipitation of clopidogrel in the non-acidic environment of the small intestine, 3) the fact that the formulation used in***

the CLARINET study was administered via naso-jejunal route in some of the neonates. It is not known whether the pediatric clopidogrel solution administered via a naso-gastric or naso-jejunal tube results in the same bioavailability as the oral administration. The sponsor did not present any data to address this issue. At present, it is not known what levels of clopidogrel are achieved when the solution is administered through these routes.

4. ***The sponsor states that the all the clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution. Therefore, these formulations are considered pharmaceutical equivalent*. The sponsor is not correct, because the concentration of the active ingredient is different (b) (4)) and the route of administration for some of the pediatric subjects was different (oral vs. naso-gastric or naso-jejunal tube), therefore, the formulations used in the pediatric program cannot be considered to be pharmaceutically equivalent. In addition of that the formulation used in the CLARINET trial also presents a potential bioavailability/bioequivalence problem. Therefore, the formulations used in the pediatric program are not pharmaceutically equivalent, nor therapeutically equivalent**.***

   Pharmaceutical Equivalents: *Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.*

   ***Therapeutic Equivalents:** Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2)they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that(a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.*

5. ***Although, the pediatric-formulation used in the BA study and the pediatric formulation used in the CLARINET pediatric-pivotal clinical trial are both solution formulations; because 1) the formulations are different, 2) the concentration of the active drug is different, 3) the percentage of (b) (4) an inactive ingredient presenting a potential bioavailability/bioequivalence problem is different, and 4) the route of administration was different for some pediatric patients; these formulations are not pharmaceutically nor therapeutically equivalent. (b) (4) .***

6. ***In conclusion, contrary to the recommendation given in the pediatric written request* that clearly states that the relative bioavailability of the formulation to-be-used in clinical studies (each study) should be characterized; the applicant never evaluated the bioavailability of the pediatric formulation used in the CLARINET trial, neither the impact that the route of administration could have on the bioavailability of this pediatric formulation.***

   Pediatric Written Request FORMULATION ISSUES
   The studies described below should use an age appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

7. ***Overall, without having the data from a bioavailability study (****i.e., four way crossover study****) evaluating; 1) the BA of the approved Plavix® tablets vs. the pediatric formulation used in the CLARINET study using the oral route of administration, 2) the BA of the approved Plavix® tablets given by oral route vs. the pediatric formulation used in the CLARINET study administered by naso-gastric tube, and 3) the BA of the approved Plavix® tablets given by the oral route vs. the pediatric formulation used in the CLARINET study administered by naso-jejunal tube, one could speculate that these differences would not result in differences in bioavailability (resulting in dissimilar exposures), but one would never be able to provide a complete answer for the following relevant questions;***

- ***WHY DID THE CLARINET TRIAL FAIL?***
- ***WAS THE FAILURE DUE TO THE USE OF AN INADEQUATE FORMULATION?***
- ***WAS THE ROUTE OF ADMINISTRATION A MAJOR CONTRIBUTOR TO THE TRIAL FAILURE?***

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

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 20-839 (b)(4) S-051, M. Rose

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

/s/

ANGELICA DORANTES
01/12/2011

PATRICK J MARROUM
01/12/2011