

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-839/S-051

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Action Summary Review



OFFICE OF NEW DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NDA: 20839/S-051

Applicant: sanofi-aventis

Indication: Plavix[®] (clopidogrel bisulfate) for prevention of death and shunt thrombosis in infants with cyanotic congenital heart disease palliated with a systemic to pulmonary artery shunt

Date: May 5, 2011

Reviewer: Stephen M. Grant, M.D. (HFD-110)

This memo conveys the Division's recommendation to approve changes proposed by sanofi-aventis to the PI for Plavix that describe the results of CLARINET, a trial of administering Plavix to prevent mortality and thrombosis-related morbidity in infants with a systemic to pulmonary artery shunt. The trial failed to demonstrate a clinical benefit. However, the failure may be the result of testing a dose of Plavix too low to have adequate anti-platelet effect and, possibly, delays in initiation of study drug following the shunt procedure. Hence it is the Division's conclusion that the failure of the trial does not preclude that platelet P2Y₁₂ ADP receptor inhibitors may be useful for this and other related indications. The approved changes in the PI clearly convey this concept.

This application has been the subject of reviews of biopharmaceutics (Dorantes; 12 January 2011), clinical pharmacology (Mishina, Krudys; 23 December 2010), clinical (Rose; 27 December 2010, 10 January 2011), statistics (Chen; 16 August 2010) and project management (Blaus; 14 January 2011). This review is derived entirely from the information and analyses contained in these reviews. In general I concur with the opinions expressed in the reviews listed above and so will discuss only areas of special import to understanding the Division's opinions.

1 Background/Summary

Section 505A of the Act [21 USC §355a] permits NDA holders to obtain an additional six months of market exclusivity (by delaying for six months the approval of any abbreviated new drug application) if the NDA holder submits requested information relating to the use of the active moiety in the pediatric population. The intent of the legislation is to encourage clinical studies in the pediatric population thereby providing health care providers with information about the appropriate use of drugs in infants and children. As described in the "Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act," the information (generally a clinical study) must be *requested* by the FDA (although interested parties may propose a pediatric study in order to solicit a request from the

FDA). Written Requests are specific and address a number of issues, as enumerated on page 5 of the guidance.

Sanofi-aventis submitted supplement 51 to their approved NDA for Plavix describing the results of the trial CLARINET, “International, randomized, double-blind clinical study evaluating the efficacy and safety of clopidogrel 0.2 mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (eg, modified Blalock Taussig shunt),” in order to obtain an additional six months of exclusivity for Plavix. Pediatric exclusivity was granted by the chair of the Pediatric Exclusivity Board (Dr. John Jenkins) on 20 January 2011.

Separate from the request for Pediatric Exclusivity, the Division held discussions with sanofi about how to describe the outcome of CLARINET in the Plavix PI. It is the opinion of the Division that defects in the design and conduct of CLARINET prevented it from providing definitive information about the utility of inhibiting platelet P2Y₁₂ ADP receptors in infants with cyanotic congenital heart disease (CCHD) palliated with a systemic to pulmonary artery shunt. Sanofi initially disagreed with the Division’s assessment and their proposed labeling changes were not acceptable. As a result, the Division sent sanofi a Complete Response letter on 14 January 2011. However, shortly after Pediatric Exclusivity was granted, the Division and sanofi agreed on making changes to the PI that incorporated the Division’s assessment.

2 Pediatric Development of Plavix

Sanofi conducted three clinical studies to support the development of Plavix for this indication.

2.1 BDR4580

BDR4580 was a clinical pharmacology study comparing the bioavailability in healthy adult males of the inactive metabolite of clopidogrel (assays for neither the active metabolite nor the parent were available at that time) after administering 75 mg of clopidogrel as the marketed tablet formulation or 75 mg of clopidogrel- [REDACTED] (b) (4) for single use. The results indicated that the bioavailability of the inactive metabolite was slightly greater for the liquid formulation.

COMMENT: The results of the study were not useful because the relationship between the concentrations of the active and inactive metabolite could not be derived and the moiety of interest is the active metabolite.

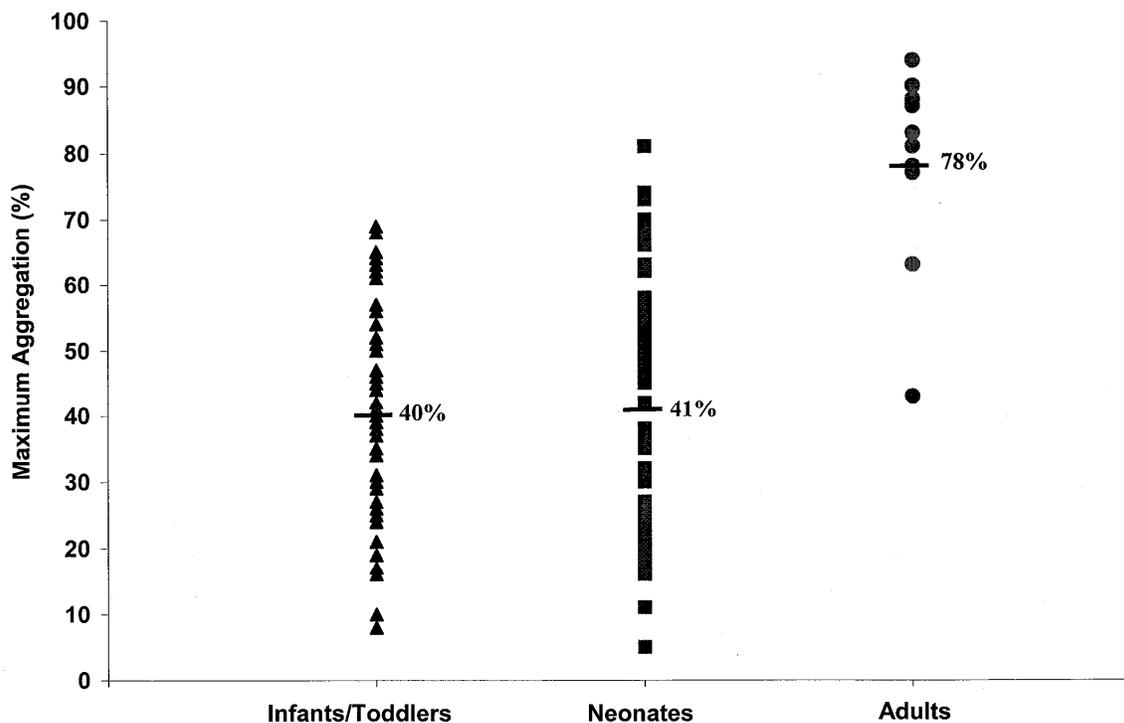
2.2 PICOLO

PICOLO was a dose ranging study of administering a second [REDACTED] (b) (4) [REDACTED] for single use in neonates and toddlers “at risk for thrombosis” (this eligibility criterion was likely related to the ethics of administering an antiplatelet agent to children). The objective was to identify a dose that resulted in a 30 to 50% relative reduction in platelet aggregation induced by 5µM ADP from baseline as measured by light transmission aggregometry (LTA). This level of reduction was targeted because that is the level of reduction seen after administration of the standard dose of Plavix to adults.

COMMENT: LTA can be difficult to perform and reproducibility among different laboratories has been a problem. The Division has had difficulty interpreting submissions containing results from these tests and has been reluctant to base regulatory actions on them.

At baseline, infants and toddlers were observed to have less platelet aggregation in response to ADP than do adults, as shown in the figure below.

**Percent Platelet Aggregation in Response to 5uM ADP
in Infants/Toddlers (n=50) vs. Neonates (N=50) vs. Adults (N=11)**



COMMENT: If this information is correct, the lower baseline ADP-stimulated aggregation in infants/toddlers and neonates indicates that ADP is a less potent agonist of platelet aggregation in this age group. If true, then a platelet P2Y12 ADP receptor antagonist such as clopidogrel may have less utility in this age group than in adults for the prevention of pathologic thrombosis. And assuming the relative reduction in platelet aggregation seen in adults after administration of clopidogrel should be the goal for choosing a dose for a study in infants and neonates was not appropriate.

As originally designed, clopidogrel doses of 0.01 mg/kg, 0.1 mg/kg, and 1.0 mg/kg (the latter is approximately the standard adult dose) were to be tested. However, at some point the DMC endorsed a recommendation from the Pharmacodynamic Assessment Committee to change the third dose tested to 0.2 mg/kg, possibly due to a significant reduction in platelet aggregation observed in subjects administered 0.1 mg/kg. 0.2 mg/kg was chosen as the dose to be administered in the confirmatory trial.

COMMENT: The rationale for choosing a dose of clopidogrel much lower than the adult dose for a population in which ADP is a less potent agonist of platelet aggregation is not clear. At a minimum, given the uncertainties of dose selection, more than one dose should have been tested in the confirmatory trial.

2.3 CLARINET

CLARINET was an event-driven, randomized, double-blind, placebo-controlled trial of administering a third formulation of clopidogrel 0.2 mg to infants with CCHD with a systemic to pulmonary artery shunt for prevention of death and thrombosis-related morbidity. The trial failed to demonstrate an effect either on the primary efficacy outcome or bleeding. The following issues cloud the interpretability of the study:

- The formulation of clopidogrel administered in CLARINET was different from either of the formulations administered in BDR4580 or PICOLO. (b) (4)

The bioavailability of this formulation was not assessed. As Dr. Dorantes notes in her review, due to the differences in composition the bioavailability of the formulation of clopidogrel administered in CLARINET may differ significantly from that of the formulation administered in BDR4580.

- The selection of the dose tested in CLARINET was not well-supported. In particular, administration of a dose only 20% of the standard adult dose does not appear prudent. At the first meeting of the Steering Committee for CLARINET, members expressed concern that the dose being tested was too low. And the Division prior to sanofi submitting the data in the figure above commented in a meeting with sanofi “if the response (of platelets to ADP) in neonates...is markedly less than in adults, the premise for the study may need to be reconsidered.”

COMMENT: When queried about the method for selecting the dose, sanofi provided answers from individuals on the Pharmacodynamic Assessment Committee so it appears that these individuals picked the method for choosing the dose. While the individuals involved are well-respected authorities, it is unusual for a company to accept the opinions of external consultants without internal input and to ignore the concerns of members of the steering committee. Of course trials conducted to obtain pediatric exclusivity are unusual in that the goal is not to obtain data to support a marketing application but rather to persuade FDA that the trial complies with the Written Request.

- There was no important difference in the rate of reported bleeding between the placebo and clopidogrel subjects, as can be seen in the table below adapted from one in Dr. Rose’s review. 20% of the placebo subjects bled so bleeding is, as expected, frequent in this population and administration of an anti-platelet agent should increase the rate of bleeding.

Incidence of bleeding by severity in CLARINET

	Placebo (N=436)	Plavix 0.2 mg/kg/day (N=464)
Any	88 (20.18%)	87 (18.75%)
Mild	53 (12.16%)	44 (9.48%)
Moderate	20 (4.59%)	24 (5.17%)
Severe ^b	15 (3.44%)	19 (4.09%)

COMMENT: Administration of clopidogrel in clinical trials always is associated with increased rates of bleeding compared to the placebo rate. In the ACTIVE-W trial the bleeding rate of subjects administered clopidogrel + aspirin (aspirin was administered to

88% of the subjects in CLARINET) was similar to that of subjects administered warfarin. The lack of excess bleeding in the clopidogrel subjects in CLARINET indicates that it is likely that the dose of clopidogrel administered in this trial had either no anti-platelet activity or minimal activity.

- Although the protocol for CLARINET stipulated “patients should be randomized and treated as early as possible following shunt placement,” most patients were randomized more than two weeks after shunt placement. If the effect of clopidogrel is greater early, at the time when the stimulus to thrombosis is greatest, then delayed randomization would have obscured a treatment effect.

COMMENT: When administered for treatment of ACS in the CURE trial, the benefit of clopidogrel appeared to be greatest in the first two months. And trials of clopidogrel for chronic CAD, such as CHARISMA, have not shown a benefit. But extrapolation of adult data from CAD trials to the very different population in CLARINET is speculative. And because it is unlikely a pharmacological dose of clopidogrel was administered in CLARINET, the data from the trial itself are uninformative.

3 Regulatory Actions

3.1 Pediatric Exclusivity

Sanofi’s request for Pediatric Exclusivity was discussed at three separate meetings of the Pediatric Exclusivity Board. As discussed in the guidance, the Board compares the Written Request to the reports of studies point-by-point. At the first meeting, while stipulating that sanofi met most of the terms of the Written Request, the Division as well as the Office of Drug Evaluation 1 Director did not support granting Pediatric Exclusivity. We felt that sanofi’s design and conduct of the trial deviated from good scientific principles in two important respects and so the terms of the Written Request had not been met.

- First, delays in enrolling subjects after shunt placement was not in accord with the protocol and may have obscured a treatment effect.
- Second, improper dose selection likely resulted in testing a dose of clopidogrel too low to be effective.

After further interactions with sanofi and two more meetings, Pediatric Exclusivity was granted. The Board was not persuaded that the delays in enrolling subjects indicated lack of adherence to the protocol because the phrase in the protocol stipulating enrollment “as soon as possible” was vague. The Board also noted that the data indicating that baseline ADP-stimulated platelet aggregation was lower in infants/toddlers and neonates were submitted to the Division and that the Division had not objected to the dose administered in CLARINET. The Division agreed sanofi had submitted a figure indicating the results, but noted that sanofi did not analyze the implications of that data nor did they engage the Division in a discussion of their import despite the Division expressing to sanofi concern about the relative effects of ADP agonism of platelet aggregation in adults versus neonates. The Division opined that sanofi would have been more diligent in selecting a dose or doses to test if a positive outcome had been important to the company. The chair stated that in the context of pediatric exclusivity, the burden for adequate study design falls to the FDA in composing the written request.

COMMENT: Drug development is a complicated process in which the Agency plays a role but is not the main actor. Compared with the Agency, sponsors have superior expertise in trial design and information about the actions of the drugs to be tested. The Agency's expertise is in the interpretation of data generated by trials, not in their design and conduct. Further, the protocols for clinical trials are frequently amended in response to observations that accumulate during their conduct and the Agency does not have access to the accumulating data. In CLARINET, the accumulating data indicating that bleeding rates were similar in both groups should have at least stimulated a discussion about whether the anti-platelet activity of the dose of clopidogrel being tested was sufficient. In my opinion, pediatric drug development will not be aided by a having a situation in which the Agency is wholly responsible for designing trials and sponsors can get valuable extensions in marketing exclusivity while being absolved of any defects in trial design.

3.2 Labeling Changes

The Pediatric Exclusivity Board members agreed with the Division that the study as conducted “did not provide interpretable data.” The Division therefore felt it was important that the Plavix PI make clear that the results of CLARINET were far from definitive and so should not discourage future research into the utility of platelet P2Y₁₂ ADP receptor antagonists for treatment of children with CCHD or other conditions in children in which thrombosis plays a role in causing mortality or serious morbidity. The original changes to the Plavix PI proposed by sanofi suggested

 (b) (4)

The final agreed-upon labeling changes are in accord with the Division's requirements.

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

/s/

STEPHEN M GRANT
05/05/2011