CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839/S-051

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER HFD-110/ Division of Cardiovascular and Renal Products

2. NDA # 20-839

3. NAME AND ADDRESS OF APPLICANT
Sanofi Aventis
55 Corporate Drive
Bridgewater, NJ 08807

4. SUPPLEMENT S-051
Date: Jul. 15, 2010

5. NAME OF THE DRUG
Plavix

6. NONPROPRIETARY NAME
Clopidogrel bisulfate

7. SUPPLEMENT PROVIDES for labeling changes in connection with a Pediatric Written Request for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease.

8. AMENDMENT
None

9. PHARMACOLOGICAL CATEGORY
Antithrombotic

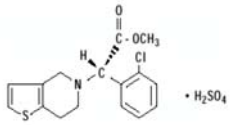
10. HOW DISPENSED
Rx

11. RELATED NDAs
None

12. DOSAGE FORM
Tablets

13. POTENCY
75 mg and 300 mg

14. CHEMICAL NAME AND STRUCTURE
Methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9.



15. COMMENTS In this Efficacy/Labeling Supplement, managed by OND, the firm has submitted labeling changes based on the results of the Phase 3 safety and efficacy study, CLARINET, in pediatric patients. The Sponsor states that the pediatric formulation they developed will not be marketed since the recommendation is not to use clopidogrel in children. In view of this, Sanofi has not submitted Module 3 and only summarized the clinical pediatric formulations used in Module 2. From a CMC perspective a detailed review is not warranted, however, since the Medical Officer has raised the issue of the bioavailability of the Phase 3 solution formulation, a consult request was made to ONDQA Biopharmaceutics to comment on this issue. See Review Notes and Dr. Dorantes' review for additional details.

16. CONCLUSIONS AND RECOMMENDATIONS Satisfactory CMC information has been submitted on the Phase 3 formulation in the Aug. 22, 2006 amendment to IND 34,663. No CMC related labeling changes are proposed. A detailed CMC review will be needed if, in the future, the sponsor submits a pediatric formulation for marketing.

17. REVIEWER NAME (AND SIGNATURE)
K. Srinivasachar

DATE COMPLETED Jan.11, 2011

Review Notes

An age-appropriate constituted oral solution of clopidogrel bisulfate was used for all pediatric clinical studies. The drug substance used in these formulations is identical to the clopidogrel bisulfate described in the NDA for Plavix tablets. The sponsor states that all clinical formulations developed and used during the pediatric program consisted of clopidogrel bisulfate in solution and therefore considered pharmaceutically equivalent. An overview of these formulations is reproduced below:

Table 2 - Formulation development overview

(b) (4)

Although all these formulations are solutions, (b) (4) The sponsor performed a bioavailability study comparing the Phase 1 formulation to the commercial Plavix 75 mg tablet and assumed that the other two formulations would have similar bioavailability. This assumption has been questioned by the Medical Officer, Dr. Martin Rose in his review dated Dec. 27, 2010 who believes the Phase 3 CLARINET formulation could have lowered bioavailability possibly due to precipitation of clopidogrel in the non-acidic environment of the small intestine. This was referred to Dr Angelica Dorantes, ONDQA Biopharmaceutics, for further input.

IND Quality Amendment dated Aug. 22, 2006:
This amendment provides complete CMC information on the Phase 3 formulation mentioned above. The drug product is a (b) (4)

(b) (4)

Conclusions: The sponsor has concluded from the studies carried out that there is no benefit from the use of clopidogrel in the pediatric population. They request a six month Pediatric Exclusivity. Other review disciplines have questioned the appropriateness of the studies carried (dose selection, bioavailability of formulation used etc.). This is not within the scope of the CMC review. What is clear is that there will be no commercial pediatric formulation at this time and consequently, no changes to the Description and How Supplied sections of the package insert labeling.

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/s/

KASTURI SRINIVASACHAR
01/12/2011

HASMUKH B PATEL
01/13/2011