# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 20-839/SE1-019

## EA/FONSI

# REVIEW

# OF

# ENVIRONMENTAL ASSESSMENT

# FOR

# NDA 20-839 / S-019

# Plavix® Tablets

# (97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)

## Division of Cardio-Renal Drug Products (HFD-110)

## Center for Drug Evaluation and Research

**Date Completed: February 11, 2002**

## EXECUTIVE SUMMARY:

**A FONSI is recommended**

Clopidogrel bisulfate (drug substance) and its metabolites are expected to enter into the aquatic environment. It and its metabolites are not volatile. They are not expected to adsorb strongly to soil or sediment. The highest expected introduction concentration in the aquatic compartment (EIC) is estimated to be 1.6 ppb based on the highest annual use estimate of 70,787 kg of clopidogrel free base. Clopidogrel is susceptible to slow hydrolysis and aerobic biodegradation. Photodegradation is not a depletion mechanism. The EIC is expected to be higher than the expected environmental concentration (EEC) due to dilution in the aquatic environment and identified depletion mechanisms. The quotient, $EC_{50}$ divided by EIC is more than 1000. Based on this information, adverse environmental impacts are not expected.

| Organism/Test | $EC_{50}$ (ppm) | NOEC (ppm) |
|---|---|---|
| | | MIC (free base) |
| Aspergillus niger | N/A | > 1000 |
| Bacillus subtilis | N/A | > 800 |
| Clostridium perfringens | N/A | > 1000 |
| Trichoderma viride | N/A | > 1000 |
| Nostoc | N/A | 200 |
| Daphnia magna ($EC_{50}$ @ 48 hours) | 8.3 ppm | 6.2 ppm |
| Daphnia magna ($EC_{50}$ @ 24 hours) | 16 ppm | |

# ENVIRONMENTAL ASSESSMENT

**Review Notes:** The EA references and summarizes reports and literature in NDA 20-839 / S-019 submitted for 75 mg Plavix® Tablets and the drug substance clopidogrel bisulfate. The tablets contain 97.86 mg clopidogrel bisulfate (drug substance) but are labeled 75 mg clopidogrel (free base).

Increased use of clopidogrel bisulfate is projected as a result of a new indication for Plavix® Tablets, a previously approved drug product. Pharmacokinetic studies demonstrated that clopidogrel bisulfate is extensively metabolized to 20 different metabolites. No individual metabolites that correspond to more than 10% of the administered dose were identified. The primary metabolites have a structure that is similar to clopidogrel. They are likely to exhibit a similar or more rapid environmental depletion rate and a lower or equivalent environmental toxicity. Therefore, clopidogrel bisulfate was used for testing because it will give the most conservative estimates of environmental fate and effects.

1. **EA Dated:** August 16, 2001 with amendment dated Feb 7, 2002
   Project Manager: Colleen LoCicero
   Chemistry Reviewer: Florian Zielinski

2. **Name of applicant/petitioner:** Sanofi-Synthelabo Inc.

   **ADEQUATE**

3. **Address:** 9 Great Valley Parkway, Malvern, PA 19355

   **ADEQUATE**

4. **Description of the proposed action:**

   a. **Requested Approval:**

   The applicant is requesting approval of an efficacy supplement to market Plavix® (clopidogrel bisulfate) Tablets (75 mg) for a new indication. The Plavix® Tablets are packaged in HDPE bottles and PVC/PVDC blister packs. The EA is submitted according to 21 CFR Part 25.

   **ADEQUATE**

**b. Need for Action:**

The product is indicated for the reduction of atherosclerotic events. The supplement provides for the use of the product to treat Acute Coronary Syndrome in humans throughout the U.S.

**ADEQUATE**

**c. Expected Locations of Use (Drug Product):**

The drug product will be used primarily in private homes and to some extent in hospitals and clinics throughout the U.S.

**ADEQUATE**

**d. Disposal Locations:**

Disposal by hospitals, pharmacies and clinics will be in accordance with their procedures. Typically, a community's solid waste management system will be used for drugs used at home. Solid waste management systems may include landfills, incineration and recycling. Minimal quantities of the unused drug could be disposed in the sewer system.

**ADEQUATE**

**5. Identification of chemical substances that are the subject of the proposed action:**

**Drug Substance:** clopidogrel bisulfate (USAN Name)

**Chemical Name:** Thieno[3,2-c]pyridine-5(4H)-acetic acid, alpha-(2-chlorphenyl)-6,7-dihydro-,methyl ester, (S)-sulfate (1:1)

**CAS Numbers:** clopidogrel bisulfate, 120202-66-6
clopidogrel (free base), 113665-84-2

**Molecular Weights:** clopidogrel bisulfate, 419.9
clopidogrel (free base), 321.8

**Molecular Form.:** clopidogrel bisulfate, $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$
clopidogrel (free base), $C_{16}H_{16}ClNO_2S$

**Structural Form:** Provided on page 5/21 of the EA.

**Melting Point:** 176.8°C by differential scanning calorimetry

**Physical Descrip.:** White to slightly cream colored powder

**ADEQUATE**

**6. Environmental Issue:**

**a. Identification of Substances of Interest**

Humans metabolize clopidogrel bisulfate to 20 metabolites that are excreted in the urine. The principal metabolite is a carboxylic derivative of clopidogrel bisulfate. About 4% of the administered dose is excreted in this chemical form. Clopidogrel bisulfate will exist in the salt form (ionic) under expected environmental conditions. Therefore, clopidogrel bisulfate rather than the free base was used in most of the environmental fate and effects studies.

**ADEQUATE**

**b. Environmental Fate of Released Substances:**

| Test | Result |
|---|---|
| Water solubility of clopidogrel bisulfate | 6.8 g/L @ pH 2.6 @ 25°C *<br>3.0 g/L @ pH 3 @ 25°C *<br>0.05 g/L @ pH 4 @ 25°C *<br>0.01 g/L @ pH 6 and 8 @ 25°C * |
| Octanol/Water Partition Coefficient<br>Log $K_{ow}$ | 3.89@ pH 7.4 @ 25°C *<br>0.59 @ pH 7.4 @ 25°C * |
| Vapor pressure | NMT 1.0 x $10^{-7}$ torr @ 25°C |
| pK | 4.55 @ 25°C * |
| Hydrolysis Rate, aq., pH 7 & 9, 25°C | 10% in 28 days (not rapid but significant) |
| Photolysis | Not observed and not expected because the absorption spectrum does not match day light |
| Aerobic Biodegradation | 4.1% degradation after 36 days, probably related to solubility changes rather than biodegradation per se. |

* The temperature was reported in a telephone conversation with Nancy Barone Kribbs (Associate Director, Drug Regulatory Affairs. Sanofi-Synthelabo Inc) on February 4, 2002 and in the amendment (SN # 67) dated February 7, 2002

Based on the test data, clopidogrel bisulfate is expected to enter the aquatic environment as ionic species. It is not expected to volatilize, adsorb strongly to soil and sediment or bioconcentrate. Photolysis is not significant. Hydrolysis and aerobic biodegradation were identified as environmental depletion mechanisms.

Data were either generated or referenced from literature sources. The test reports were provided in the amendment dated February 7, 2002. The testing appears to be scientifically sound and adequate.

**ADEQUATE**

**c. Environmental Concentrations:**

The highest expected environmental introduction concentration (EIC) for clopidogrel bisulfate is 1.6 ppb based on a 5-year forecast of 70,787 kg in 2006.

**ADEQUATE**

**d. Environmental Effects:**

| Organism/Test | $EC_{50}$ (ppm) | NOEC (ppm) |
|---|---|---|
| | | MIC (free base) |
| Aspergillus niger | N/A | > 1000 |
| Bacillus subtilis | N/A | > 800 |
| Clostridium perfringens | N/A | > 1000 |
| Trichoderma viride | N/A | > 1000 |
| Nostoc | N/A | 200 |
| Daphnia magna ($EC_{50}$ @ 48 hours) | 8.3 ppm | 6.2 ppm |
| Daphnia magna ($EC_{50}$ @ 24 hours) | 16 ppm | |

The test reports were provided in the amendment dated February 7, 2002. The testing appears to be scientifically sound and adequate.

The applicant also reported human and mammalian effects (e.g. carcinogenicity study). These data are evaluated during the NDA review. Therefore, they were not evaluated as part of the EA review.

The assessment factor, namely EIC divided by $EC_{50}$ (Daphnia magna) is greater than 1000

indicating that environmental effects are not expected.

**ADEQUATE**

**7. Mitigation measures:**

The applicant briefly describes routine mitigation measures (production controls, wastewater treatment, etc).

**ADEQUATE**

**8. Alternatives to the proposed action:**

Two actions are listed (1) approval of the action through issuance of a FONSI or (2) non-approval and notification of the intent to prepare an EIS. Based on the information provided, a FONSI may be issued.

**ADEQUATE**

**9. List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

The preparers and contributors are identified and a brief description of their qualifications was provided.

**ADEQUATE**

**10. References:**

References are provided.

**ADEQUATE**

**Appendices:**

Confidential appendices containing production estimates and formulation information are provided. Test reports were provided in the amendment dated February 7, 2002.

The EA is appropriately identified with confidential and non-confidential sections.

**ADEQUATE.**

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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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Melissa Maust
2/13/02 03:22:42 PM
ENV ASSESSMENT

FONSI recommended

Florian Zielinski
2/13/02 03:26:31 PM
ENV ASSESSMENT

Nancy Sager
2/13/02 03:48:20 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
2/15/02 03:22:19 PM
CHEMIST
concurred

# ENVIRONMENTAL ASSESSMENT

# AND

# FINDING OF NO SIGNIFICANT IMPACT

# FOR

# NDA 20-839 / S-019

## 75-mg Plavix® Tablets

## (97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)

**Division of Cardio-Renal Drug Products (HFD-110)**
**Center for Drug Evaluation and Research**

**Date Completed: February11, 2002**

## FINDING OF NO SIGNIFICANT IMPACT

**NDA 20-839 / S-019**

**75-mg Plavix® Tablets**
**(97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)**

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Plavix® Tablets, Sanofi-Synthelabo Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact of the use and disposal from use of clopidogrel bisulfate. Clopidogrel bisulfate is currently approved for the reduction of atherosclerotic events. This supplement provides for the use of Plavix® Tablets in treating Acute Coronary Syndrome in humans throughout the U.S.

Clopidogrel bisulfate and its metabolites are expected to enter the aquatic environment. They are not volatile and are not expected to adsorb strongly to soil or sediment. Clopidogrel bisulfate is susceptible to slow hydrolysis and aerobic biodegradation. The results of toxicity studies indicate that clopidogrel bisulfate and its metabolites are not expected to be toxic to aquatic organisms at expected environmental concentrations.

Plavix® Tablets will be used by patients in their homes and in hospitals and clinics. American hospitals and clinics will dispose empty or partially empty packages according to their standard operating procedures. Typically, a community solid waste management system will be used for drugs administered at home. The community solid waste management system may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Appended Electronic Signature Page

## 4.1 ENVIRONMENTAL ASSESSMENT

# TABLE OF CONTENTS

**4.1 Environmental assessment**

This Environmental Assessment was written to address the environmental impact of PLAVIX® and its drug substance clopidogrel bisulfate for which the Chemistry, Manufacturing, and Controls (CMC) data were described in NDA 20-839 (submitted to IND 34,663, Serial No. 170, 14 March 1997) and in the NDA 20-839/S-009 (31 March 2000).

Increased use of clopidogrel bisulfate is projected as a result of a new indication for PLAVIX®, a previously approved drug. Estimates of maximum forecasted annual production of the drug in the next five years and an estimate of Maximum Expected Emitted Concentration (MEEC) are provided in the Environmental Assessment appendices, Confidential appendix, MEEC calculation, (Section 4.1.11.3).

**4.1.1 Date**

16 August 2001

**4.1.2 Name of applicant**

Sanofi-Synthelabo Inc.

**4.1.3 Address**

DMF Holder: Sanofi Chimie
9 Rue Du President Allende
94256 Gentilly
France

Orgamol S.A.
Evionnaz
CH 1902
Switzerland

Contact for FDA: Sanofi-Synthelabo Inc.
Drug Regulatory Affairs
9 Great Valley Parkway
Malvern, PA 19355
USA

**4.1.4 Description of the proposed action**

**4.1.4.1 Description of the requested approval**

Sanofi-Synthelabo Inc. is requesting approval per section 505(b) of the Food, Drug and Cosmetic Act for the use of PLAVIX® (clopidogrel bisulfate) for the treatment of Acute

Coronary Syndrome. PLAVIX® is produced as 75 mg tablets and packaged in white, high-density polyethylene (HDPE) bottles or clear (PVC/PVDC)/blister packs. An Environmental Assessment (EA) is submitted pursuant to 21 CFR, part 25.

**4.1.4.2 Need for the proposed action**

PLAVIX® is an inhibitor of platelet aggregation and antithrombitic agent for the treatment of acute coronary syndrome. PLAVIX® appears to have an antiplatelet aggregation mode of action by modification of the platelet adenosine diphosphate (ADP) receptor.

**4.1.4.3 Location where the product will be used**

The drug product is intended for use in, and will be distributed to hospitals, pharmacies, and clinics for use by patients in their homes throughout the United States.

Empty or partially empty packages generated at U.S. hospitals, pharmacies or clinics will be disposed of according to site waste disposal procedures either by the generator or after return to Bristol-Myers Squibb or Sanofi-Synthelabo facilities.

Out-of-specification, unused or outdated PLAVIX® drug product returned for disposal to Bristol-Myers Squibb or Sanofi-Synthelabo are currently packaged, shipped, and incinerated as industrial, non-hazardous wastes according to applicable environmental regulations.

Hospitals, pharmacies, clinics, and individual patients in the home may also dispose of empty or partially empty containers of drug product as part of their community waste management system, which may include landfills, incineration, or recycling. Minimal quantities of unused drug waste generated in the home could be disposed via the sewer system.

***4.1.5 Identification of chemical substance that is the subject of the proposed action***

This Environmental Assessment was written using preclinical data and environmental fate and effects testing on PLAVIX® and its drug substance clopidogrel bisulfate described in NDA 20-839 (submitted to IND 34,663, Serial No. 170; Information Amendment: Chemistry, Manufacturing, and Controls) and in the NDA 20-839/S-009 (31 March 2000).

**4.1.5.1 Nomenclature**

Established Name (USAN) for Drug Substance: Clopidogrel bisulfate

Product Tradename: PLAVIX®

CAS Number: 120202-66-6 (clopidogrel bisulfate)
113665-84-2 (clopidogrel base)

USAN: methyl (*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1)
methyl (+)-(*S*)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine- 5-(4*H*)-acetate, sulfate (1:1)

CAS Name (clopidogrel bisulfate):
Thieno [3,2-c] pyridine-5 (4*H*)-acetic acid, alpha-(2-chlorphenyl)-6,7-dihydro-, methyl ester, (*S*)-,sulfate (1:1)

IUPAC Name: (*S*)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5yl)-acetic acid methyl ester

INN: Clopidogrel

Synonyms: Clopidogrel, clopidogrel hydrogen sulfate

Internal code: SR25990C (clopidogrel bisulfate)
SR25990 (clopidogrel base)

**4.1.5.2 Molecular formula**

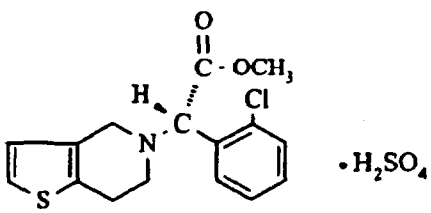
$C_{16}H_{16}Cl\,NO_2S \bullet H_2SO_4$ (clopidogrel bisulfate)
$C_{16}H_{16}Cl\,NO_2S$ (clopidogrel base)

**4.1.5.3 Molecular weight**

419.9 (clopidogrel bisulfate)
321.8 (clopidogrel base)

**4.1.5.4 Physical and chemical data**

Structural formula:



$\bullet H_2SO_4$

Appearance: White to slightly cream-colored powder

Bulk density: 0.40 g/ml untapped
0.53 g/ml tapped

Melting point (determined by differential scanning calorimetry): 176.8°C

Vapor pressure at 25°C: < 1.33 x $10^{-5}$ Pascals (< 1.0 x $10^{-7}$ Torr)

Solubility in water: (at 25°C) 1mg/ml or
6.8 g/l at pH = 2.6
3.0 g/l at pH = 3
0.05 g/l at pH = 4
0.01 g/l at pH = 6
0.01 g/l at pH = 8

Solubility in solvents:

Table (4.1.5.4) 1 - Solvent solubility of clopidogrel bisulfate

| Solvent | Solubility (g/l at 20°C) | Descriptive Term (USP and Ph. Eur.) |
|---|---|---|
| Methanol | 459 | Freely soluble |
| Ethanol | 52 | Soluble |
| Methylene chloride | 15 | Sparingly soluble |
| Dioxane | 2.4 | Very slightly soluble |
| Ethyl ether | 0.01 | Practically insoluble |

Partition coefficient octanol/water: ($K_{ow}$ at pH = 7.4) 3.89 @25°C 1mg/ml or
Log $K_{ow}$ at pH = 7.4: 0.59

UV visible absorption: 195, 270, and 277 nm (buffer pH = 3)
193 nm (buffer pH = 7)
198 nm (buffer pH = 10)

Dissociation constant (pKa): 4.55 @ 25°C 1mg/ml or

Hydrolysis rate (aqueous, 28 day): 10% at pH of 7 and 9 at 25°C

**4.1.5.5 Health and safety data (clopidogrel bisulfate)**

Table (4.1.5.5) 1 - Health and Safety

| Assessment | Value |
|---|---|
| Sanofi-Synthelabo exposure band | 0.02- 0.1 mg/m$^3$ |
| Dust explosion minimum ignition energy | 10-25 mJ |
| Minimum dust cloud ignition temperature | 440-460°C |
| A/B dust flammability classification | Group A (Flammable) |

### 4.1.5.6 Toxicity data

- **Acute exposure**

Table (4.1.5.6) 1 –.Toxicology data

| Route | Test | Species | Results |
|---|---|---|---|
| Oral | $LD_{50}$ | Rat | ≥ 2 g/kg |
| Oral | $LD_{50}$ | Mouse | ≥ 2 g/kg |
| Oral | $LD_{50}$ | Baboon | > 2 g/kg |
| Intravenous | $LD_{50}$ | Rat | 110 mg/kg |
| Intravenous | $LD_{50}$ | Mouse | 160 mg/kg |

- **Effects of repeated\chronic exposure**

PLAVIX® is known to prolong bleeding time and platelet aggregation in the clinic.

- **Developmental and reproductive toxicity**

Reproduction studies in rats and rabbits at 65 and 78 times the recommended human dose showed no evidence of impaired fertility or fetal toxicity.

In another study, clopidogrel was found to have no effect on fertility of male and female rats at up to 52 times the recommended human dose.

- **Genotoxicity**

Table (4.1.5.6) 2 - Genotoxicity

| Test | Test System | Results |
|---|---|---|
| Ames | *Salmonella typhimurium*<br>*E.Coli* | Negative |
| DNA repair test | Rat hepatocytes | Negative |
| Forward gene mutation | (CHO/HGPRT) | Negative |
| Chromosomal aberration | (CHO cells) | Negative |
| Mouse micronucleus test | Mouse micronucleus | Negative |

- **Carcinogenicity**

There was no evidence of tumorigenicity in 78-week rat and 104-week mouse studies with plasma exposures 25 times that in humans at the recommended dose of 75 mg/day clopidogrel.

### 4.1.5.7 Environmental data

- **Oxygen demand**

COD: 1,260 g $O_2$/kg clopidogrel bisulfate
ThOD: 1,520 g $O_2$/kg clopidogrel bisulfate
BOD: Not determined because of low water solubility at test pH (7.0)

- **Aerobic biodegradation**

Aerobic biodegradation in water:
4.1 % after 36 days

- **Environmental effects**

Table (4.1.5.7) 1 - Clopidogrel bisulfate environmental effects test summary

| Test and Test Organism | Toxicity Concentration |
|---|---|
| Microbial Growth Inhibition | |
| *Bacillus subtilis* | 800 ppm |
| *Nustoc muscorum* | 200 ppm |
| *Aspergillus niger* | > 1000 ppm |
| *Trichoderma viride* | > 1000 ppm |
| *Clostridium perfringens* | > 1000 ppm |
| *Daphnia* Acute Toxicity | |
| *Daphnia magna* 24 hour $EC_{50}$ | 16 ppm |
| *Daphnia magna* 48 hour $EC_{50}$ | 8.3 ppm |
| *Daphnia magna* 48 hour NOEC | 6.2 ppm |

- **Additives**

A listing of additives to the drug substance to formulate drug product is described in the Environmental Assessment appendices, Confidential appendix – composition of drug product (Section 4.1.11.2). The physical/chemical properties and environmental data for the additives are also detailed in the Environmental Assessment appendices, Confidential appendix – composition of drug product (Section 4.1.11.2).

#### 4.1.6 Environmental issues

The CDER Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, July 1998 (FDA EA Document), was used to develop strategies for evaluating the environmental fate and effects of the proposed action.

The substance of interest, clopidogrel bisulfate, was identified from pharmacokinetic studies. Environmental fate and effects studies were then performed on clopidogrel bisulfate.

**4.1.6.1 Environmental fate of the released substances**

- **Identification of substances of interest**

Pharmacokinetic studies have demonstrated that clopidogrel is extensively metabolized. Following repeated administration of clopidogrel (10 to 150 mg/day for 14 to 16 days), the concentration of unmetabolized clopidogrel was below the limit of detection at doses up to 100 mg/day. Clopidogrel is inactive *in vitro* and is considered a bioprecursor since it needs metabolic activation to express activity.

Human and animal studies indicated 20 metabolites of clopidogrel bisulfate. The principal circulating metabolite is SR26334, a carboxylic acid derivative of clopidogrel bisulfate. SR26334 is inactive when dosed orally or IV. After administration of 400 mg of clopidogrel bisulfate, about 4% of SR26334 was excreted in urine.

No metabolites were identified which are excreted in concentrations greater than 10% of dose. The primary identified metabolites have a similar chemical structure to clopidogrel bisulfate. As such, they are likely to exhibit a similar or more rapid environmental depletion rate and an equivalent or lower environmental toxicity than the parent. Because of these considerations, fate and effects testing was performed on the parent compound clopidogrel bisulfate.

- **Physical and chemical properties of clopidogrel bisulfate**

Physical and chemical properties were determined for clopidogrel bisulfate. They are summarized (Environmental Assessment appendices, Non-confidential appendix – Data Summary Table for Clopidogrel Bisulfate, Section 4.1.11.1) and discussed in detail below.

**- Solubility @ 25°C** JWZ 2/4/02

Clopidogrel bisulfate showed low solubility in water in the environmental pH range. The solubility of anhydrous clopidogrel bisulfate in various solvents was also determined. Upon consideration of other physical and chemical fate data, it is apparent that clopidogrel bisulfate would migrate to the water compartment despite its relatively low water solubility.

**- Dissociation constant @ 25°C** JWZ 2/6/02

The dissociation constants were determined using potentiometry methods. The compound dissociated at one dissociation constant; 4.55 ($pk_1$), indicating an ionized species will exist within the environmental pH range.

**- Partition coefficient** @25C 4/02 2/n/o~

The partition coefficient log $K_{ow}$ = 0.59 was determined by potentiometry methods. This value indicates little or no tendency to bioconcentrate or sorb significantly into organic materials such as soils, aquatic or terrestrial life forms.

**- Vapor pressure**

The vapor pressure was measured at 25°C by the gas saturation method at < $1.33 \times 10^{-5}$ Pascal (< $1.0 \times 10^{-7}$ Torr). This negligible value indicates that clopidogrel bisulfate is not likely to volatilize from water or as a solid.

**- UV/visible absorption spectrum**

The UV spectrum performed in aqueous buffer media over a wavelength range of 190-900 nm showed an absorption band with the following maximum absorption wavelengths:

195, 270, and 277 nm (pH = 3 buffer)
193 nm (pH = 7 buffer)
198 nm (pH = 10 buffer)

This indicates light absorption occurs outside of the spectral range associated with daylight, thus photodegradation does not offer a likely mechanism for degradation.

- **Environmental depletion mechanisms of clopidogrel bisulfate**

Abiotic and aerobic biodegradation studies were conducted to evaluate the biodegradation depletion mechanism for the drug substance in the environment. They included the Hydrolysis Rate, Aerobic Biodegradation, and Chemical Oxygen Demand (COD).

**- Hydrolysis rate**

The hydrolysis rate of the drug substance was investigated in aqueous media at a pH of 7 and 9 at 25°C and 50°C. Ten percent hydrolysis was observed after 28 days at pH = 7 and 9 at 25°C, indicating that hydrolysis in the environmental temperature and pH range is not a rapid depletion mechanism.

**- Aerobic biodegradation**

The aerobic biodegradation in water study indicated 4.1 percent biodegradation occurring after 36 days. The test report indicates that the measured biodegradation may be related to the changing solubility of clopidogrel in the test system rather than biodegradation.

**- Biochemical oxygen demand**

The biochemical oxygen demand could not be determined because the water solubility of clopidogrel bisulfate was lower than the test protocol requirement.

**- Chemical oxygen demand and theoretical oxygen demand**

The chemical oxygen demand and theoretical oxygen demand are listed below.

COD = 1,260 g $O_2$/kg clopidogrel bisulfate
ThOD = 1,520 g $O_2$/kg clopidogrel bisulfate

- **Summary of environmental depletion mechanisms of clopidogrel bisulfate**

Fate data do not show a rapid depletion mechanism for clopidogrel bisulfate in the environment. These data indicate that the drug substance will migrate into the aquatic compartment in the undegraded form. After entry into the aquatic compartment, fate studies indicate non-rapid degradation by hydrolysis and aerobic biodegradation.

- **Expected environmental concentration for clopidogrel base**

The expected environmental concentration (EEC) and the Expected Introduction Concentration (EIC) are described in Section 4.1.6.5. The EIC and EEC are not expected to differ, except from dilution in the aquatic environment since no rapid depletion mechanism was identified and sorption and bioaccumulation are not indicated.

The Maximum Expected Emitted Concentration (MEEC) value for clopidogrel base was calculated using the estimated highest annual quantity of production for all indications in any of the next five years. See Environmental Assessment appendices, Confidential appendix - MEEC calculation (Section 4.1.11.3).

- **Summary of environmental fate of clopidogrel bisulfate**

*Based on the water solubility and low vapor pressure, clopidogrel bisulfate exhibits no* discernible tendency to volatilize and migrate into the atmospheric compartment from the solid state or while diluted in aqueous solutions. Water and solvent solubility, vapor pressure, partition coefficient and dissociation constant data indicate that the drug substance will migrate to the aquatic compartment. Based on the low partition coefficient (log $K_{ow}$ = 0.59), the drug substance exhibits no discernible tendency to bioconcentrate in aquatic or terrestrial life forms.

After entry into the aquatic compartment, fate studies indicate non-rapid degradation by hydrolysis and aerobic biodegradation.

**4.1.6.2 Environmental effects of the released substances**

Studies summarized below have been conducted to identify the effects of the drug substance into the environment.

- **Human and mammalian effects**

**- Acute toxicity**

The estimated $LD_{50}$ for an oral dose of clopidogrel bisulfate was the same for rats, mice, and baboons (> 2 g/kg). For intravenous administration, the estimated $LD_{50}$ values were similar in both rats (110 mg/kg) and mice (160 mg/kg).

**- Chronic toxicity**

Carcinogenicity studies - Clopidogrel bisulfate is considered to be non-tumorogenic based upon a 78-week mouse study and a 104-week rat study.

Reproductive toxicity - Clopidogrel bisulfate showed no effect on fertility in a rat study. No evidence of impaired fertility or fetal toxicity was shown in other studies in rats and rabbits.

Genotoxicity - Clopidogrel bisulfate was negative in all genotoxicity tests including the Ames/*Salmonella typhimurium/E. coli* mutagenicity assay, an *in vivo* mouse micronucleus assay, a forward gene mutation assay (CHO/HGPRT), a DNA repair test (rat hepatocytes) and a chromosomal aberration assay (CHO cells).

- **Environmental effects studies**

The available fate data indicate that the drug substance will migrate to the aquatic compartment. Consequently, all toxicity studies were performed in the water compartment. The tiered approach in the FDA EA Document was used to direct study of the effects of the drug substance on life forms in the aquatic compartment. Fate data indicates that microbial inhibition test was recommended. The log $K_{ow}$ value indicated that Tier 1 testing (acute toxicity, one species) should be performed. In accordance with the guideline, the *Daphnia* acute toxicity test was performed. The environmental effects test data for clopidogrel bisulfate are summarized below.

**- Microbial inhibition**

The microbial inhibition study produced a threshold inhibition level of 200 ppm for *Nostoc sp.* This is an indication that the drug substance has a low tendency to inhibit the activity of microbes in the aquatic environment.

- ***Daphnia* acute toxicity**

The *Daphnia* acute toxicity study produced an $EC_{50}$ (median effective concentration) at 24 hours of 16 ppm, an $EC_{50}$ at 48 hours of 8.3 ppm and a No Observed Effect Concentration (NOEC) of 6.2 ppm.

**4.1.6.3 Use of resources**

- **Materials**

All materials used in the drug substance/product manufacturing and distribution are readily available and will not cause depletion of any natural resources that are in short supply.

- ***Effects upon endangered species and historic places***

The production, distribution and use of clopidogrel bisulfate substance, PLAVIX® product, and the disposal of associated wastes will have no impact on threatened or endangered species.

Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by the clopidogrel bisulfate or PLAVIX® production or distribution activity or any related waste disposal.

**4.1.6.4 Summary of fate and effects of emissions in the production and distribution cycles**

The expected emissions from the clopidogrel bisulfate chemical and pharmaceutical manufacturing and distribution processes will be in compliance with the measures to protect the environment as defined by laws and regulations.

It is predicted that the atmospheric, aquatic and terrestrial ecosystems, and the human health will not be affected deleteriously by clopidogrel bisulfate manufacturing or distribution. This is based upon consideration of regulatory compliance, manufacturing process controls, fate and effect studies, waste and materials management, safe work practices, hazard communication, and other procedures.

As described in Section 4.1.4.3, all returned goods wastes are disposed at off-site permitted facilities, in accordance with existing environmental regulations. Hospitals and offices may also dispose of unused drug product as a part of their medical waste disposal procedures according to environmental regulations.

**4.1.6.5 Summary of fate and effects of emissions during patient use**

The drug product is intended to be distributed to hospitals, clinics and pharmacies for use by patients in their homes throughout the United States.

The primary route of entry of clopidogrel bisulfate into the environment will be via human excretions. Pharmacokinetic studies indicate there is significant evidence of drug product transformation in humans. However, calculations were made assuming that clopidogrel bisulfate will enter into Publicly Owned Treatment Works (POTW) in an unmetabolized form since its primary metabolites are of a similar or a simpler chemical structure and can be expected to be equally or more rapidly depleted and have an equivalent or lower environmental toxicity than the parent. The low vapor pressure and octanol/water partition coefficient ($K_{ow}$) and the solubility characteristics of the drug substance indicate that it will remain in the water compartment with no migration to the atmospheric compartment. The drug substance exhibits no discernible tendency to bioconcentrate in aquatic or terrestrial life forms based on the low partition coefficient (log $K_{ow}$ = 0.59).

Fate data do not indicate a rapid depletion mechanism for clopidogrel bisulfate in the environment. However, non-rapid degradation was indicated in hydrolysis and aerobic biodegradation studies.

The Maximum Expected Emitted Concentration (MEEC) value for clopidogrel base was calculated using the estimated highest annual quantity of production for all indications in any of the next five years. The aquatic compartment expected introduction concentration (EIC) formula is described in the FDA EA Document. The MEEC is the EIC or the expected environmental concentration (EEC), which ever is greater. In this case, the EIC is the greater value which conservatively assumes that all clopidogrel base production enters and is discharged to the environment from a POTW at the same concentration. The MEEC was calculated as shown in the Environmental Assessment appendices, Confidential appendix - MEEC calculation (Section 4.1.11.3).

Per the FDA EA Guidance Document, compounds with an $EC_{50}$ / MEEC concentration ratio (the assessment factor) greater than 1,000 will provide an adequate testing endpoint. The $EC_{50}$ / MEEC concentration ratio for clopidogrel base, ($EC_{50}$ = 8.3 ppm) exceeds 1,000, indicating that there is no need for additional testing. The data also indicate that there will be no significant environmental impact from clopidogrel in the concentration at which it will appear in the environment.

**4.1.6.6 Summary of the fate and effects of emissions from disposal**

Since wastes from patient use are disposed at incineration, landfill, or other facilities regulated by the EPA or State agencies which consider environmental impacts from waste disposal, the Expected Introduction Concentration (EIC) for disposal does not need to be calculated and further evaluation of environmental fate and effects of emissions from disposal does not need to be made.

**4.1.7 Mitigation measures**

Environmental impacts associated with the manufacturing, shipment, distribution, use, and waste disposal of the drug substance clopidogrel bisulfate and drug product PLAVIX® will be made negligible through the use of appropriate control measures as required by permitting and other procedures and regulatory requirements.

**4.1.8 Alternative to the proposed action**

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of the proposed action will provide an important benefit to patients in need of treatment for acute coronary syndrome with no significant environmental risk.

**4.1.9 List of contributors and preparers**

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**4.1.10 References**

Data presented in the previous pages were obtained from the following sources:

The Merck Index 9th ed., 1989.

Material Safety Data Sheets, from the data bank of the Canadian Center for Occupational Health & Safety

N. Irving Sax, Dangerous Properties of Industrial Materials, 8th ed.

Registry of Toxic Effects of Chemical Substances (RTECS)

Ullman's Encyclopedia of Industrial Chemistry, 5th ed., 1987

Suppliers Material Safety Data Sheets

Data from Sanofi Chimie

Data from Sanofi Synthelabo Recherche

Data from Sanofi Synthelabo Research Division

Study reports from Chilworth Technology

Study reports from Springborn Laboratories

### 4.1.11 Environmental assessment appendices

### 4.1.11.1 Non-confidential appendix - data summary table for clopidogrel bisulfate

Table (4.1.11.1) 1 - Data summary table for clopidogrel bisulfate

| | |
|---|---|
| **Physical/ Chemical Characterization** | |
| Water solubility<br>@ 25C Aug 2/n/ov | 6.8 g/l at pH = 2.6<br>3.0 g/l at pH = 3<br>0.05 g/l at pH = 4<br>0.01 g/l at pH = 6<br>0.01 g/l at pH = 8 |
| Solvent solubility (g/l) | |
| Methanol | 459 |
| Ethanol | 52 |
| Methylene chloride | 15 |
| Dioxane | 2.4 |
| Ethyl ether | 0.01 |
| Dissociation constant ($pK_a$) | 4.55 @ 25°C |
| Octanol/Water partition coefficient (Log $K_{ow}$) | 0.59 at pH= 7.4 @ 25C Aug 2/n/ov |
| Vapor pressure at 25°C (Pascals) | < $1.33 \times 10^{-5}$ |
| Bulk density: | 0.40 g/ml untapped<br>0.53 g/ml tapped |
| **Depletion Mechanisms** | |
| UV visible absorption peaks (nm) | 195, 270, and 277 nm (buffer pH = 3)<br>193 nm (buffer pH = 7)<br>198 nm (buffer pH = 10) |
| Hydrolysis rate (aqueous, 28 day) | 10% at pH of 7 and 9 at 25°C |
| Aerobic biodegradation in water | 4.1 % after 36 days |
| **Environmental Effects** | |
| Microbial Growth Inhibition | |
| *Bacillus subtilis* | 800 ppm |
| *Nustoc muscorum* | 200 ppm |
| *Aspergillus niger* | > 1000 ppm |
| *Trichoderma viride* | > 1000 ppm |
| *Clostridium perfringens* | > 1000 ppm |
| *Daphnia* Acute Toxicity | |
| *Daphnia magna* 24 hour $EC_{50}$ | 16 ppm |
| *Daphnia magna* 48 hour $EC_{50}$ | 8.3 ppm |
| *Daphnia magna* 48 hour NOEC | 6.2 ppm |

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