

**Executive CAC****Date of Meeting :** July 22, 2003**Committee:** David Jacobson-Kram, Ph.D., HFD-024, Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Abigal Jacobs, Ph.D., HFD-540, Member  
C. Joseph Sun, Ph.D., HFD-570, Alternate member  
Albert DeFelice, Ph.D., HFD-110  
Belay Tesfamariam, Ph.D., HFD-110, Presenting Reviewer**Author of Minutes:** Belay Tesfamariam

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

**IND number:** 63,449  
**Drug name:** CS-747 (LY 640315)  
**Sponsor:** Eli Lilly & Co., Indianapolis, IN**Background:** CS-747 is a member of thienopyridine class of antiplatelet agents. It is an inhibitor of ADP-induced platelet aggregation by direct inhibition of ADP binding to its receptor. CS-747 is a prodrug that is de-esterified to form an active metabolite that irreversibly inhibits P2Y<sub>12</sub> ADP receptor and thus prolong bleeding time. Bleeding is a potential risk that may be expected with CS-747 due to the mechanism of action of inhibition of platelet aggregation.**Rat Carcinogenicity Study Protocol and Dose Selection:**

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 10, 30, 100, or 300 mg/kg/day for 3- and 6-month study in Fisher 344 rat (n=10-15). At 100 mg/kg, body weight gain was decreased by 17 % and 19% in males and females, respectively. Prothrombin times and activated partial thromboplastin times (APTT) were prolonged in rats receiving  $\geq 100$  mg/kg. Slight anemic tendencies in the group treated with  $\geq 100$  mg/kg and slight increases of reticulocyte ratio in female rats treated with 300 mg/kg were observed. Prothrombin and activated partial thromboplastin times were prolonged rats treated with  $\geq 100$  mg/kg, and fibrinogen levels were increased in the 300 mg/kg group. Histopathological examination revealed hypertrophy of the hepatocytes in the  $\geq 30$  mg/kg group. These changes are consistent with enzyme induction. The maximal tolerated dose (MTD) is estimated to be 100 mg/kg/day. The AUC<sub>0-24</sub> of the active metabolite (R-138727) at the MTD is about 189-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in the Fischer 344 rat at oral doses of 0, 10, 30, and 100 mg/kg/day (n=55/sex/group). The vehicle to solubilize CS-747 is 0.5 % w/v tragacanth solution. Animals in the control group will receive the vehicle (0.5% w/v tragacanth solution).

**Executive CAC recommendations and Conclusions:**

The Committee concurred with the proposed doses of 0, 10, 30, 100 mg/kg/day, based on MTD (decrease in body weight) and a variety of toxicities, including irreversible inhibitor of platelet function and thus prolong bleeding time.

**Mouse Carcinogenicity Study Protocol and Dose Selection:**

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 100, 300, or 1000 mg/kg/day for 3-month study in Crj:B6C3F1 mice (n=10). Doses of 1000 mg/kg/day caused decrease body weight gain by 46 to 62%. In the 300-mg/kg group, the primary effects were suppression of body weight gain by 16 and 28% in males and females, respectively, increased liver weight, and hypertrophy of the centrilobular hepatocytes. Doses of 100 mg/kg/day did not cause overt toxicity, although increased liver weight was observed. Hematology revealed decrease in red blood cell count, hemoglobin, hematocrit and MCHC and increase in reticulocyte ratio and MCV in the 1000 mg/kg group. The MTD is estimated to be 300 mg/kg/day. The AUC<sub>0-24</sub> of the active metabolite (R-138727) and primary human inactive metabolite (R-106583) at the MTD were > 265-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in Crj:B6C3F<sub>1</sub> mice at oral dose of 0, 30, 100 and 300 mg/kg/day (n=55/sex/group). Organs and tissues of all animals will be fixed with phosphate buffered formalin for histopathology examination. Representative examples of normal and abnormal findings will be photographed when drug-related changes are observed.

**Executive CAC recommendations and Conclusions:**

The Committee concurred with the proposed doses of 0, 30, 100, 300 mg/kg/day, based on decrease in body weight gain at three months and decrease in RBC count at 300 mg/kg/day. It was also noted that the active metabolite exposure ratio is quite high (about 200:1).

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
- (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
- (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
- (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

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/Division File, HFD-110  
/Team leader, HFD-110  
/Reviewer, HFD-110  
/CSCO/PM, HFD-110  
/ASeifried, HFD-024

## **Executive CAC**

**Date of Meeting:** 2/26/2008

**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair  
Paul Brown, Ph.D., OND IO, Member  
John Leighton, Ph.D., DDOP, Alternate Member  
Albert DeFelice, Ph.D., DCRP, Team Leader  
Belay Tesfamariam, Ph.D., DCRP, Presenting Reviewer

**Author of Minutes:** Belay Tesfamariam, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA #:** 22-037  
**Drug Name:** Prasugrel (CS-747)  
**Sponsor:** Eli Lilly & Co., Indianapolis, IN

### **Background:**

Prasugrel (CS-747) is a prodrug, member of the thienopyridine class that is de-esterified to form an active metabolite that irreversibly inhibits platelet P2Y<sub>12</sub> purinergic receptor, and thus prolongs bleeding times. All circulating metabolites in humans occurred in the circulation of the nonclinical species. No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay, and *in vivo* mouse micronucleus test.

### **Mouse Carcinogenicity Study:**

The mouse carcinogenicity study was conducted at doses up to 300 mg/kg which yielded systemic exposures of prasugrel metabolites of about 500-fold greater than the anticipated clinical exposures. The doses were adequately high in that an MTD was achieved in the 300 mg/kg groups as indicated by body weight decreases of 9 - 11% of controls. Necropsy revealed treatment-related changes in the liver that may be related to the tumor and non-tumor lesions. Centrilobular hypertrophy and a tendency for an increase in the incidence of eosinophilic altered cell foci were observed suggesting that hepatic drug-metabolizing enzyme induction was involved in the liver lesions. Histopathology revealed an increase in the incidence of hepatocellular adenoma in males dosed at the high dose (300 mg/kg) and in females dosed at mid and high doses (100 or 300 mg/kg). Thus, there was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (190 times human exposure).

### **Rat Carcinogenicity Study:**

The rat carcinogenicity study was conducted at doses up to 100 mg/kg which yielded systemic exposures of prasugrel metabolites greater than 50-fold than the anticipated clinical exposures. The doses were adequately high in that an MTD was achieved in the 100 mg/kg groups as indicated by body weight decreases of 11 - 13% of controls. Prasugrel did not induce treatment-related tumors in any of the organs/tissues. Prasugrel neither decreased the survival rate nor induced any specific tumor or non-tumor deaths. Necropsy revealed treatment-related changes in the liver, lung and trachea, and they were related to the non-tumor lesions which may be related to hepatic drug-metabolizing enzyme induction. Thus, in the rat there was no significant evidence of treatment-related tumors in a 2 year study with prasugrel exposures ranging to about 50 times the recommended therapeutic exposures in humans.

### **Executive CAC Recommendations and Conclusions:**

#### **Rats:**

- \* The Committee determined that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- \* The Committee determined that the study was negative for drug related tumors.

#### **Mouse:**

- \* The Committee determined that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- \* The Committee determined that the study was positive for hepatocellular adenomas in both sexes.

David Jacobson Kram, Ph.D.  
Chair, Executive CAC

cc:\

/Division File, DCRP  
/Albert DeFelice, PhD, Team leader, DCRP  
/Belay Tesfamariam, PhD, Reviewer, DCRP  
/Meg Pease-Fye, CSO/PM, DCRP  
/ASeifried, OND IO

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/s/

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Belay Tesfamariam  
4/28/2008 10:48:58 AM  
PHARMACOLOGIST  
PharmTox Review

Albert Defelice  
4/28/2008 01:26:50 PM  
PHARMACOLOGIST

Tertiary Pharmacology Review

**By:** Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology  
OND IO

**NDA:** 22-307

**Submission date:** December 26, 2007

**Drug:** prasugrel (Effient)

**Sponsor:** Eli Lilly & Co.

**Indication:** Antithrombotic therapy in subjects with acute coronary syndrome

**Reviewing Division:** Division of Cardiovascular and Renal Products

**Comments:** The pharm/tox reviewer and supervisor found the nonclinical information submitted for prasugrel to be sufficient to support the use of a 10 mg daily dose as antithrombotic therapy in subjects with acute coronary syndrome.

The reviewer proposes pregnancy category B for the labeling. Embryofetal studies did not reveal any drug-related fetal effects. Therefore, pregnancy category B is appropriate. I recommend that the labeling include appropriate CFR prescribed wording for pregnancy category B.

There was no evidence of drug related tumors in a rat carcinogenicity study. An increase in hepatocellular adenomas in both sexes was noted in a mouse carcinogenicity study in which prasugrel was administered orally. These tumors occurred in males at a dose of 300 mg/kg and in females at doses of 100 mg/kg and higher. The dose of 100 mg/kg in the mouse produced exposure to the primary metabolite of prasugrel that was approximately 190 times higher than the exposure to this metabolite in humans taking the 10 mg dose. Exposure to this metabolite in humans is greater than to the parent or other metabolites and so using AUC values for this metabolite provides conservative comparisons. Hepatocellular adenomas are not uncommon tumors in mice particularly when accompanied by hepatocellular hypertrophy and altered cell foci associated with high-dose enzyme induction as in the study with prasugrel. In some studies with other drugs where this has occurred, the human significance of the apparent drug-related mouse liver adenomas has been described as unknown. The clinical reviewer has noted a possible signal for increased tumors in clinical trial subjects taking prasugrel. That information should be carefully considered regardless of the outcome of the animal studies.

I concur with the Division pharm/tox conclusion that the nonclinical data support approval of this NDA.

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Paul Brown  
6/19/2008 12:54:22 PM  
PHARMACOLOGIST

**ADDENDUM****PHARMACOLOGY/TOXICOLOGY REVIEW***In Vitro and In Vivo Tumor Progression Studies*

**NDA number:** 22-307  
**Date Received by Center:** 1/27/2009 (electronic submission)  
**Sponsor:** Eli Lilly & Co., Indianapolis, IN  
**Reviewer name:** Belay Tesfamariam, Ph.D.  
**Division name:** Cardiovascular and Renal Products, HFD #: 110  
**Review completion date:** 2/2/2009

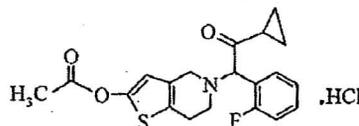
**Drug:**

**Trade name:** Effient®  
**Generic name:** Prasugrel.HCl  
**Code name:** CS-747  
**Chemical name:** 2-Acetoxy-5-( $\alpha$ -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

CAS registry number: 389574-19-0

Molecular formula: C<sub>20</sub>H<sub>20</sub>FNO<sub>3</sub>S.HCl; Molecular weight: 409.9

Structure:



**Drug class:** ADP receptor antagonist (P2Y<sub>12</sub> purinergic receptor).  
**Intended clinical population:** Antithrombotic agent in patients with acute coronary syndrome  
**Clinical formulation:** Tablets (10 mg).  
**Route of administration:** Oral  
**Disclaimer:** Tabular and graphical information are constructed by the sponsor unless cited otherwise.  
**Studies reviewed within this submission:** *In vitro* and *in vivo* cell proliferation assays.

## Introduction

### **Brief overview of carcinogenicity studies of prasugrel** (from NDA 22-307 Review, 4/26/08):

No genetic toxicity was observed for prasugrel in *in vitro* bacterial mutation and Chinese hamster lung chromosomal aberration assays, and *in vivo* mouse micronucleus test. In a 2 year rat study, there was no evidence of treatment-related tumors with prasugrel exposures ranging to about 50 times the human exposure. In a 2 year mice study, there was an increased incidence of hepatocellular adenomas at the high dose which was >250-fold higher than the human exposure. There were no other treatment-related increases in tumors in other organs. One prominent observation is that prasugrel caused hypertrophy of hepatocytes and proliferation of smooth endoplasmic reticulum, changes that are consistent with microsomal enzyme induction. Thus, the drug-induced enzyme induction may be associated with the liver adenomas. In the rat and mouse, there were high incidence of spontaneous carcinomas (liver, lung, thyroid, adrenal) but these were not enhanced by treatment with prasugrel suggesting that prasugrel may not cause tumor promotion or progression.

Additional studies were requested by the Agency to evaluate the effects of prasugrel metabolites on tumor progression using *in vitro* human tumor cell lines and *in vivo* congenitally immunodeficient 'nude' mice (10/17/08). In response to the request from the Agency, the sponsor evaluated the effects of prasugrel metabolites (R-138727 and R-106583, active and inactive metabolites, respectively) using the following models:

- I. *In vitro* effects of R-138727 and R-106583 on proliferation of human cell lines derived from lung, colon and prostate tumors.
- II. *In vivo* effects of prasugrel on growth of human tumor xenografts derived from lung, colon and prostate in 'nude' mice.

### **Summary of findings:**

- *In vitro* exposure of serum-starved human tumor cell lines (lung, colon and prostate) to prasugrel metabolites did not increase cell proliferation relative to starved cells stimulated to proliferate by addition of 10% fetal bovine serum (FBS).
- *In vivo*, tumor growth rates were not enhanced by treatment with prasugrel in tumor-bearing 'nude' mice implanted with lung, colon and prostate human tumor cells.
- In the context of the negative findings in the genotoxicity and the 2-year rodent carcinogenicity bioassays, these additional data on tumor progression assays add to the weight-of-evidence that prasugrel exhibits neither carcinogenic nor tumor progressing activity.