NDA 22,307
Prasugrel
Stent Thrombosis Results in TRITON
Karen A. Hicks, Medical Officer

Review of Supplemental Stent Thrombosis Reports

Materials Reviewed:

- NDA 22,307, Prasugrel
  Sequence 0069
  Correspondence Date: 12/5/2008
  Date Received: 12/5/2008
  Date Review Completed: 1/5/2009

- NDA 22,307, Prasugrel
  Sequence 0081
  Correspondence Date: 1/15/2009
  Date Review Completed: 1/20/2009

- NDA 22,307, Prasugrel
  Sequence 0084
  Correspondence Date: 1/29/2009
  Date Received 1/29/2009
  Date Review Completed: 1/30/2009

ERRATUM: REVIEWER RECOMMENDATIONS, #2, page 4 of the Original Review dated February 2, 2009, 08:09:02 pm.

CHANGE

REVIEWER RECOMMENDATIONS:

FROM:

2. I do NOT recommend short-term use of prasugrel or a switching strategy at a particular time point from prasugrel to clopidogrel because such a strategy has not been studied to date. Based on the stent thrombosis results, most cases of stent thrombosis in the clopidogrel treatment group occurred within the first 30 days, while most cases of stent thrombosis in the prasugrel treatment group occurred > 24 hours to 30 days. I would be especially concerned about any switch that took place within the first 30 days, because any substantial change in inhibition of platelet aggregation could convey an increased risk of stent thrombosis. Patients should only be switched from prasugrel to clopidogrel if they cannot tolerate prasugrel.

TO:

2. I do NOT recommend short-term use of prasugrel or a switching strategy at a particular time point from prasugrel to clopidogrel because such a strategy has not been studied to date. Based on the stent thrombosis results, most cases of stent thrombosis in the clopidogrel treatment group occurred within the first 30 days of the index procedure, while most cases of stent thrombosis in the prasugrel treatment group occurred within 24 hours and from > 30 days to 1 year of the index procedure. I would be especially concerned about any switch that took place within the first 30 days, because any substantial change in inhibition of platelet aggregation could convey an increased risk of stent thrombosis. Patients should only be switched from prasugrel to clopidogrel if they cannot tolerate prasugrel.

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

/s/

Karen Hicks
5/13/2009 09:02:35 AM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Secondary Review of Cancer Adverse Events and Risk/Benefit

NDA:	22,307
Drug:	prasugrel (Effient)
Indication:	reduction of atherothrombotic events and stent thrombosis in acute coronary syndromes managed by percutaneous coronary intervention
Sponsor:	Eli Lilly and Company
Review date:	May 6, 2009
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader

Background

This review is a special secondary review of the findings in this NDA submission related to cancer adverse events and risk/benefit. I initiated the analyses because of my assignment as the clinical reviewer for the prasugrel IND, a professional interest in exploring cancer rates in large outcome trials, and the suggestive results (in my interpretation) of the mouse carcinogenicity study. Because my preliminary analysis raised the issue of increased cancer rates with prasugrel in a large outcome study, the Cross Discipline Team Leader for this submission requested that I complete and formally submit my analyses. For a general background on prasugrel and this NDA submission and discussions of the formulation issues, please see the primary clinical review, the other discipline primary reviews, and the Cross Discipline Team Leader review. This version is an updated version based on a series of exchanges with the sponsor regarding the cancer events, including the data collected by the sponsor in response to those exchanges, and the discussions at the meeting of the Cardiovascular and Renal Drugs Advisory Committee on February 3, 2009; it replaces all prior versions.

Recommendation and Conclusions

I recommend approval of prasugrel for the indication of reduction in myocardial infarctions in acute coronary syndromes managed by percutaneous coronary interventions with a boxed warning regarding cancer and a duration of treatment limited to 30 days. In the large outcome study TAAL, new solid cancer rates were more than 40% higher in the prasugrel group than in the clopidogrel control group. The solid cancer rates began diverging after about 4 months and continued diverging for the duration of the study. They were associated with substantial death rates. It is impossible to decide whether these findings are real drug effects or artifactual or chance variations from TAAL alone; another study is needed. Until such a study is completed I believe it is prudent to approve prasugrel, because of its beneficial impact upon an important endpoint (myocardial infarction), but to limit its duration of use. The sponsor is planning another large outcome study in acute coronary syndrome patients who are medically managed. A description of the TAAL cancer results must be incorporated into the informed consent for the new trial, patients with active cancers or recent signs or symptoms consistent with a solid cancer must be excluded, complete follow-up for cancer events must be detailed, and the trial must be sized (preferably event driven) to have 90% power of detecting a 50% increase in the rate of development of new solid cancers. For cancer rates similar to those in TAAL, i.e., a control rate of about 1% per year, the number of events needed is about 279. A 22,000 patient trial with mean follow-up of a year and minimum follow-up exceeding 8 months should suffice.

Materials Used in Review

1. Submissions for NDA 22,307, particularly the reports and data sets for the rodent carcinogenicity studies, the data sets and case report forms for the large TAAL outcome trial, and the supplementary regulatory responses on neoplasms from March 25 through November 12, 2008
2. Primary Clinical review by Karen A. Hicks, M.D., dated December 28, 2008
3. Statistical Review of the Rodent Carcinogenicity Studies by Mohammad Atiar Rahman, Ph.D., dated February 19, 2008
4. Pharmacology/Toxicology Review by Belay Tesfamariam, Ph.D., dated April 26, 2008
5. Cardiovascular and Renal Drugs Advisory Committee Briefing Document and Powerpoint Presentations, Eli Lilly and Company

Relevant Chemistry and Metabolism

Prasugrel is a thienopyridine prodrug for an irreversible antagonist of the platelet $P2Y_{12}$ receptor. It is functionally and structurally similar to the approved thienopyridine platelet $P2Y_{12}$ receptor antagonist clopidogrel and, in fact, the large TAAL outcome trial in this submission compared prasugrel to clopidogrel rather than placebo. However, prasugrel is neither structurally nor metabolically identical to clopidogrel as shown in the structure diagrams in Figure 1 and Figure 2 and the metabolic pathways of prasugrel in Figure 3 and the major and active metabolites of clopidogrel in Figure 4.

Figure 1: Prasugrel Structural Formula

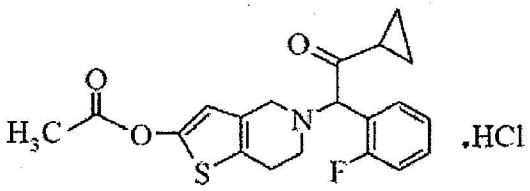


Figure 2: Clopidogrel Structural Formula

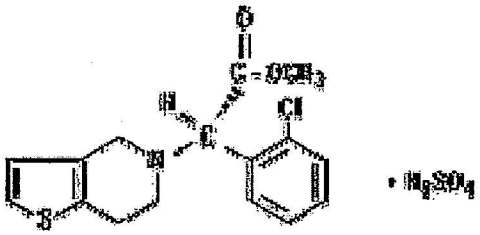


Figure 3: Prasugrel Proposed Metabolic Pathways

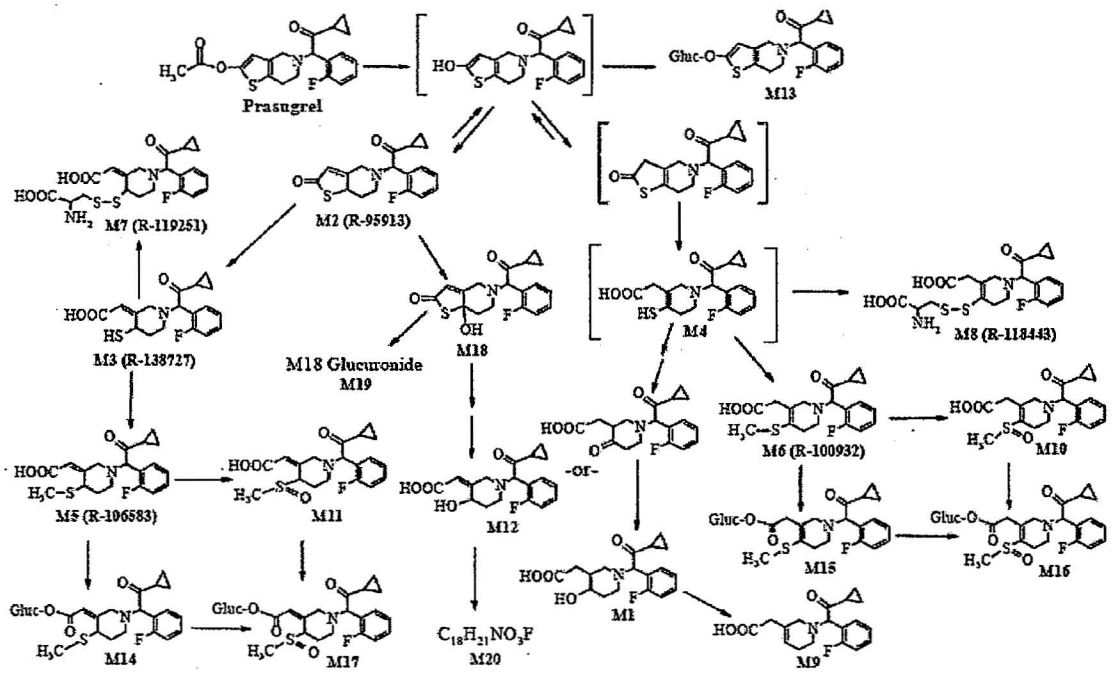
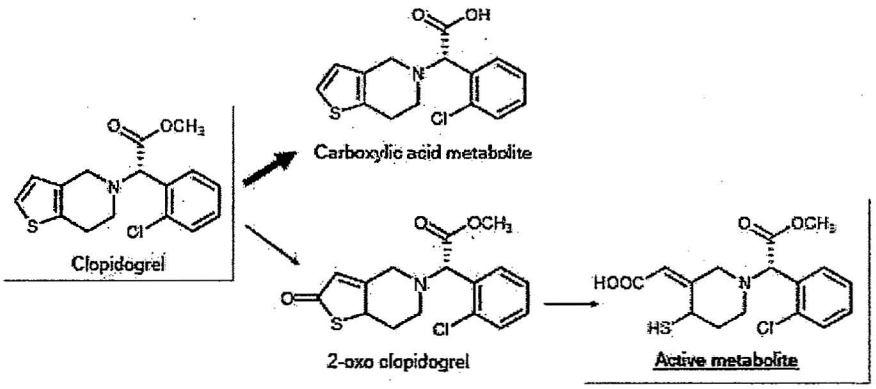


Figure 4: Clopidogrel Major and Active Metabolites*



*from http://www.inertsil.com/Technical_Data/Titansphere/ASMS2006/A061099.pdf

Both prasugrel and clopidogrel are prodrugs. Prasugrel is rapidly hydrolyzed to the inactive metabolite R-95913. R-95913 is then converted by various CYP isoenzymes to the thiol active metabolite R-138727. Clopidogrel undergoes rapid hydrolysis to its carboxylic acid derivative, the major metabolite in plasma. It also undergoes an alternate pathway of oxidation through CYP isoenzymes to a thiol active metabolite. Both prasugrel and clopidogrel undergo extensive other metabolism.

COMMENT: While structurally similar, there are sufficient structural and metabolic dissimilarities between prasugrel and clopidogrel such that an adverse affect of one can not be automatically assumed to be an adverse effect of the other. The metabolic pathways of each are diverse enough that one can not elucidate from typical clinical or pre-clinical studies what metabolite can produce an adverse effect.

Rodent Carcinogenicity Studies

Included in the NDA submission are two two-year carcinogenicity studies, one in mice and one in rats. The studies are similar, each with 55 animals per dosing and control groups, except that the dosages are lower in the rat study because of a lower tolerability limit in rats compared to mice: The mice dosages tested were 30, 100, and 300 mg/kg and the rat dosages were 10, 30, and 100 mg/kg. The suggestive carcinogenicity findings are predominantly in the mouse study. I show the distributions of neoplasms (benign and malignant) by site, sex, and dosing group in Table 1 and by sex and dosing group for both sexes combined in Table 2.

Table 1: Neoplasms with Frequency > 4 by Site, Sex, and Dosing Group in the Prasugrel Mouse Carcinogenicity Study (NOTE: All Group Sizes Were 55)

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Harderian gland	5	3	7	6	5	8	2	2
Intestinal cancer	0	2	2	1	1	0	0	2
Liver adenoma	5	5	20	39	20	11	26	44
Liver carcinoma	1	4	2	5	11	12	13	16
Liver cancer*	2	6	3	5	11	15	14	17
Liver hemangioma	1	2	0	0	6	3	1	1
Lung adenoma	1	2	4	3	5	5	5	6
Lung cancer	2	2	1	2	3	3	8	4
Lymphorecticular ca	19	24	20	16	5	12	4	6
Pituitary adenoma	2	3	4	3	1	0	0	0
Skin benign	2	0	0	1	2	0	0	1
Skin cancer	4	1	2	2	0	0	1	0
Spleen sarcoma	1	3	0	1	0	0	1	0
Spleen hemangioma	2	3	0	1	4	0	1	0
Uterus neoplasm†	1	3	3	2	0	0	0	0

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

Table 2: Neoplasms with Frequency > 4 by Site and Dosing Group in the Prasugrel Mouse Carcinogenicity Study

Group	Control	30	100	300
Harderian gland	10	11	9	8
Intestinal cancer	1	2	2	3
Liver adenoma	25	16	46	83
Liver carcinoma	12	16	15	21
Liver cancer*	13	21	17	22
Liver hemangioma	7	5	1	1

Group	Control	30	100	300
Lung adenoma	6	7	9	9
Lung cancer	5	5	9	6
Lymphorecticular ca	24	36	24	22
Pituitary adenoma	3	3	4	3
Skin benign	4	0	0	2
Skin cancer	4	1	3	2
Spleen sarcoma	1	3	1	1
Spleen hemangioma	6	3	1	1
Uterus neoplasm†	1	3	3	2

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

In addition to the neoplasms, there were two other hepatic histologic findings worth noting, shown in Table 3.

Table 3: Other Hepatic Histologic Findings in the Prasugrel Mouse Carcinogenicity Study

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Central hypertrophy	0	0	0	0	0	0	9	22
Altered cell focus, eosinophilic	6	6	18	36	9	17	23	24

Prasugrel is an enzyme inducer that, in mice, produces an increase in liver size. The central hepatocytic hypertrophy seen in the male mice at the higher dosages (mild to moderate at the 100 mg/kg dosage and moderate in 7 mice at the 300 mg/kg dosage) is attributed to this enzyme induction. (See also the discussion regarding carcinogenicity in the Comment below.) The National Toxicology Program has suggested that presence of the altered cell foci may form part of weight-of-evidence considerations used by regulatory bodies when accompanied by a concomitant liver tumor response. (Maronpot, Harada et al. 1989)

COMMENT: The most striking finding is the increase in liver adenomas. This neoplasm appears to have a high background rate in this species—note the 20 adenomas in the male control group, although this number appears to be anomalously high. While the increase in adenomas is the most statistically significant finding, the increase in the closely related liver carcinomas is also striking. Whether one counts only carcinomas or all cancers (there were also more cases of hemangiosarcomas and hepatomas in the prasugrel groups) the increase in liver malignancies is roughly 50% with prasugrel. There are also more cases of lung cancer and intestinal cancer in the prasugrel groups with suggestions of dose-response relationships.

The FDA's statistical reviewer of these studies judged the increases in adenomas and combined adenomas and carcinomas to be statistically significant: The standard statistical analysis showed statistically significant positive dose-response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes. Pairwise comparisons showed statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and mid and high dose groups in females

compared to their respective controls. (Per the Society of Toxicologic Pathology the incidences of benign and malignant neoplasms arising from the same cell type are usually combined for statistical analyses. (Boorman, Dixon et al. 2004)) The Executive CAC judged the mouse study to be positive for hepatocellular adenomas in both sexes.

I have the following additional comments on this study:

- *An increase in the rates of the most prevalent cancers of 50% or more is not consistent with the sponsor's explanation of the findings, that the liver adenoma increases are the result of enzyme induction similar to that seen with phenobarbital.*

- *The increase in uterine neoplasms, mainly polyps, by itself wouldn't appear very concerning or even unlikely—one more polyp in the control group would make all of the groups indistinguishable. However, it is consistent with the one suggestive finding in the rat study.*

- *The increase rates of altered cell foci may be consistent with the increased rates of adenomas. However, the triumvirate of liver adenoma increases, altered cell foci increases, and cancer increases appears consistent with a tumor promotion effect.*

- *Skin cancers and combined skin neoplasms were more frequent in the control group.*

While the increases in cancers with prasugrel are not statistically significant, they do not appear to be random effects. There are no comparable random increases in cancers for the placebo group. The neoplasms for which the count in the placebo group is higher are skin neoplasms, liver hemangiomas, and spleen hemangiomas. The fewer liver and spleen hemangiomas in the prasugrel groups are hardly reassuring because there are more hemangiosarcomas in these organs in the prasugrel groups.

The prasugrel rat carcinogenicity study does not show an increased rate of liver adenomas. Nor does it show any increased rates of cancers with prasugrel, either by site or in total. To the contrary, it showed lower rates with prasugrel for two malignancies: large granular lymphocytic leukemia and mesothelioma as shown in Table 4. The one finding consistent with the mice study findings is a higher rate of uterine neoplasms (due to high rates of polyps) in the prasugrel groups as also shown in Table 4.

Table 4: Neoplasms Differing by Dosing Group in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Leukemia	14	13	6	1	8	8	3	2
Mesothelioma	0	0	0	0	4	3	1	1
Uterus neoplasm	20	26	29	30				

Exposure to prasugrel and its metabolites differed between the two rodent carcinogenicity studies. The exposures for the active metabolite and the main human metabolite are shown in Table 5.

Table 5: Exposure (Mean AUC_{0-24} µg·h/mL) for Main/Active Metabolites in the Prasugrel Carcinogenicity Studies (Compared to Human 0.3/0.05 for 10 mg Daily Dose)

	Female				Male			
	10	30	100	300	10	30	100	300
Mouse		23/6	85/26	201/68		23/2	87/16	206/41
Rat	4/7	18/28	43/59		4/5	7/14	22/58	

Main human metabolite R-106583/active metabolite R-138727

In addition to the neoplasms, the similar findings to the two other hepatic histologic findings found in the mouse study were also observed in the rat study as shown in Table 6.

Table 6: Other Hepatic Histologic Findings in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Diffuse hypertrophy	0	0	0	15	0	0	0	20
Altered cell focus, eosinophilic	27	31	31	36	43	41	44	51

COMMENT: The rat carcinogenicity does not support the mouse study in suggesting that prasugrel is carcinogenic. Alone it might be interpreted as suggesting that prasugrel has a protective effect, e.g., the lower rates of leukemia. There are some similarities between the two studies for other findings, such as the endometrial polyps and the hepatocytic hypertrophy. There are also definite differences in exposure, both regarding the higher high dose exposure in the mice and the different ratios of active to main metabolite.

Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species. The difference in measured exposures between the mouse and humans is not completely reassuring because we have no idea of what metabolite could be carcinogenic. The rat study is not supportive of carcinogenicity but neither does it contradict the possibility. However, by itself the results of the mouse study do not prohibit approval—the critical issue is what the human studies show. Regardless, these studies are very useful for hypothesis generation: The hypothesis they suggested to me is that prasugrel may be a tumor promoter for a variety of solid cancers—it is this hypothesis that I tested in my initial analysis of the TAAL study data.

Cancer Adverse Events in TAAL

The only human study in the submission large and long enough to provide any insight into cancer rates is TAAL. Hence I limit my analyses to that study.

TAAL (or TRITON) was a large, international, multicenter, randomized, double-blind, double dummy, active-controlled (vs. clopidogrel) trial of prasugrel in patients with ACS undergoing PCI. TAAL compared prasugrel 60 mg loading, 10 mg maintenance to the labeled dosages 300 mg loading, 75 mg maintenance for clopidogrel (although the administration of the loading dose was delayed until after angiography in patients with UA/NSTEMI—not the usual practice for