COMMENT: The site-reported events portray a slightly different picture of prasugrel benefit than the CEC adjudications. For the composite site-reported endpoint (all cause death/MI/stroke) corresponding to the CEC-adjudicated primary endpoint (CV death/MI/stroke), the TAAL results are not statistically significant for the pre-specified primary analysis in UA/NSTEMI patients. However, in the UA/NSTEMI patients the point estimate is beneficial for prasugrel and in all patients there is a statistically significant improvement in the site-reported death/MI/stroke endpoint by unstratified analysis. The benefit in all analyses appears to be a reduction in MIs. However, the site-reported events show a lower absolute benefit, a suggestion that deaths may be problematic, and little evidence of benefit beyond 15-30 days.

I interpret these efficacy results as showing that prasugrel has a small (in the order of one event/100 patients) early (< 30 days) benefit related to reduction in MIs. Whether the benefit increases beyond 30 days is less clear but it is very clear that significant bleeding increases continuously with time and the potential for tumor promotion remains a serious question for long term use.

Discussion

I interpret all of these results as follows: The preclinical studies suggest, but are not conclusive, that prasugrel is a tumor promoter in mice. The clinical results in TAAL are also suggestive of a promoter effect. While it is tempting to dismiss the clinical findings as due to ascertainment bias due to increased bleeding with prasugrel, the delay in the divergence of the incidence plots for four+ months, the continued divergence of most plots through 16 months, the lack of evidence for an ascertainment bias for solid tumors other than GU, the cancer deaths leaning in the wrong direction, and the lack of a similar ascertainment bias in CHARISMA do not support the ascertainment bias hypothesis.

Besides drug effect, one other possible explanation is a play of chance resulting in more cancer prone individuals ending up in the prasugrel group. While this remains possible, I think it is unlikely because of the size of TAAL, the excellent balance in cancers reported as on-going at baseline, and the significant p values for the most relevant comparisons (0.024 and 0.0013). While these p values do not have the same strength of evidence as that of a pre-specified primary efficacy endpoint, neither were they picked as unusual from data dredging the trial results. The p value of 0.024 is generated by the initial analysis I had envisioned based on my review of the pre-clinical data.

One limitation of TAAL is the quality of the data. TAAL was not pre-specified to examine cancer rates, although cancer events are routinely captured in most CV trials and were captured prospectively in TAAL. TAAL did not capture prospectively a complete history of all cancers. However, from a patient perspective, a cancer recurrence is as deadly as or usually more deadly than a new cancer—prasugrel looks as bad for new and worse solid cancers as it does for new solid cancers. So the data quality issue (the lack of cancer histories) that some reviewers have viewed as insurmountable does not make the TAAL cancer results uninterpretable. TAAL raises a serious safety concern. I don't think that safety concern can be put to rest by manipulating TAAL data; another study is needed.

I am not impressed at all by the counterargument that the finding lacks biologic plausibility because we have never seen a similar pattern before. We have no large randomized trials of documented tumor promoters in humans. We should not assume that we know exactly what to expect based on animal studies. The evidence for a problem is far stronger in TAAL than it was at NDA submission times for the recent withdrawals from market, such as Vioxx and Zelnorm.

The efficacy data from TAAL document a reasonable benefit on reduction in MIs. However, there is no overall mortality benefit and there is little evidence of a benefit beyond 15-30 days. I can argue that the short term benefit justifies immediate approval, although only for short term use, but I can also argue that approval should be delayed until the planned trial in medically managed ACS addresses the cancer promotion issue.

One issue that I have not discussed is the formulation problem of conversion from salt to base form. Please see the FDA CMC and CDTL reviews for the details on this problem. Because I would project that cancer promotion should not have a steep dose-response relationship, the formulation problem is not important for the cancer issue. It could affect other safety and efficacy and hence is relevant to risk/benefit analyses. My overall judgment is that, because TAAL showed efficacy and acceptable non-cancer related safety despite a less than ideal formulation, the formulation problem should not be an absolute bar to approval. However, it is another factor that argues for delaying full approval until the sponsor addresses all outstanding issues with new data and a new formulation.

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/s/

Thomas Marciniak
12/31/2008 02:15:55 PM
MEDICAL OFFICER
This review replaces completely my review from June 2008.

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Secondary Review of Cancer Adverse Events

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:	June 12, 2008
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader

Background

This review is a special secondary review of the findings in this NDA submission potentially related to cancer adverse events. 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 submission and findings and issues other than those related to cancer, please see the primary clinical review, the other discipline primary reviews, and the Cross Discipline Team Leader review.

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 strong recommendation that treatment with prasugrel be limited to 3-30 days duration. In the large outcome study TAAL, new solid cancer rates were about 50% 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 small increases in cancer deaths. It is impossible to decide whether these findings are real drug effects 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 recommended duration of use should be determined by a quantitative absolute risk-benefit analysis over the first 30 days. 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 a history of solid cancers must be excluded, complete follow-up for cancer events must be detailed, and the trial must be sized (including a blinded interim analysis of cancer event rates with resizing if needed) to have 90% power of detecting a 50% increase in the rate of development of new solid cancers.

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 dated March 25, 2008, and May 9, 2008
2. Primary Clinical review by Karen A. Hicks, M.D., dated April 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

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

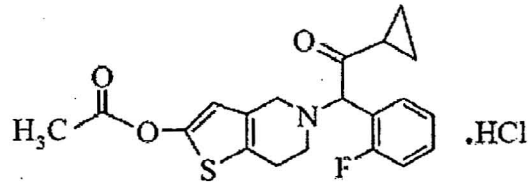


Figure 2: Clopidogrel Structural Formula

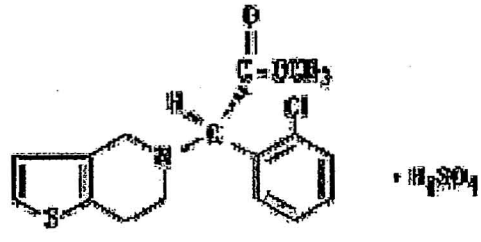


Figure 3: Prasugrel Proposed Metabolic Pathways

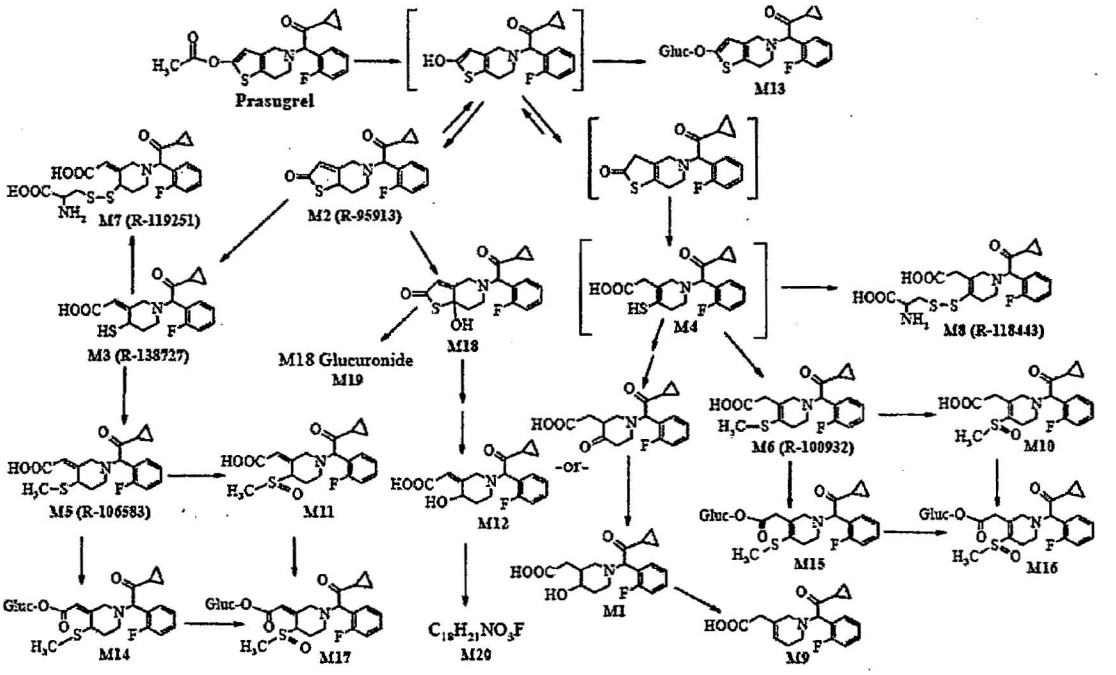
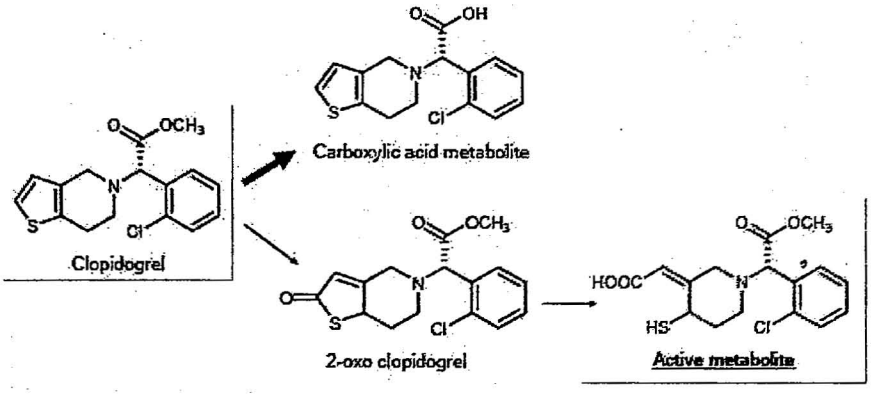


Figure 4: Clopidogrel Major and Active Metabolites*



*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.

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. 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.*

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.