This would seem to make causality less likely. In the entire history of drug development, the only products thought to stimulate tumor development are the recombinant erythropoietins (Epoetin alfa; Darbepoetin alfa), and these are growth factors, whereas prasugrel is not.

3. Tumor Types

The distribution of tumor types was typical of a coronary artery disease patient population, and appeared little affected by prasugrel. According to United States Cancer Statistics, National Program of Cancer Registries, the leading types of cancer by incidence are: prostate, breast, lung/bronchial, and colorectal (http://apps.nccd.cdc.gov/uscs/, searched 7/2/08). In TAAL, the numbers of new non-benign tumors in these categories for prasugrel and clopidogrel were prostate: 11 versus 9; breast: 5 versus 1; lung/bronchial: 17 versus 13; and colorectal: 23 versus 10, respectively. Because females comprised only ~25% of the subjects enrolled in TAAL, the numbers of breast cancer cases would be roughly doubled if extrapolated to a 50% female population. Thus, if prasugrel is causally related to the excess tumors observed in TAAL, the stimulation appears to be fairly general in nature.

4. Carcinogenicity; Tumor Promotion

Considering the biology of the tumor types observed and the relatively brief (15-month) time frame of TAAL, it is simply not plausible for carcinogenicity to underlie these trends. Moreover, the results of prasugrel's carcinogenicity studies were not regarded to be positive (except by Dr. Marciniak, who held a minority view). Thus, if prasugrel *is* playing a role here, it is through enhancement of tumor progression and not carcinogenesis. The *in vitro* and *in vivo* data do not, however, support the hypothesis that prasugrel promotes tumor growth and/or progression.

5. Cancer Deaths

There were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (95% CI: 0.79, 2.55). If cancer deaths in subjects with pre-existing cancers are included in the totals, the numbers of deaths are 33 and 21, respectively (RR=1.57, 95% CI: 0.91, 2.71). The applicant has argued that the imbalance is a byproduct of ascertainment bias. Because there were greater numbers of subjects with neoplasia-related adverse events in the prasugrel group (175) than the clopidogrel group (138), and because vital status was specifically sought for this subgroup of subjects, the imbalance in deaths would be expected to approximate 175/138 = 1.27. In fact, the RR for cancer deaths exceeds 1.27, although it is not strikingly different. Thus, the applicant's argument does provide some measure of reassurance. Nevertheless, deaths are always a reason for concern.

6. Multiplicity of Safety Analyses

Safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity; therefore, there is always the possibility of a false positive finding. False positive results are, of course, *expected* under these circumstances. Beyond a mere association between prasugrel and excess cancers, therefore, biological plausibility, exposure-response, and other factors are helpful to support causality, and these factors seem to be missing here.

Conclusion:

In summary, by the Division's classification of non-benign tumors, there is a trend showing more adverse events of new, non-benign neoplasms in the prasugrel group than the clopidogrel group. The relative risk is 1.29, with 95% CI: 0.96, 1.72. The absolute risk is 0.33%, over a median follow-up of 12 months. However, given the lack of a plausible underlying mechanism of action, non-clinical data that fail to show tumor promotion, the multiplicity of safety analyses, the fact that fairly extensive data on a related drug (clopidogrel) show no signal, and the reality that only the erythropoietins have been shown to promote tumors, there is a good chance that these observations are spurious.

There is unanimous agreement within the Division that these findings should not stand in the way of prasugrel's approval, and the Office concurs with this position. However, there are differing opinions in the Division as to how labeling should be handled. There are some who argue that if there is a risk of tumor stimulation, it should be related to exposure. These individuals advocate placing a limit on the duration of prasugrel use to perhaps 30 days, with patients switching to clopidogrel at that point. Counter-arguments have been raised to this proposal: 1) Any proposed duration of treatment is necessarily arbitrary; 2) Switching involves logistical issues. Some patients will simply discontinue their thienopyridine, which could lead to stent thrombosis; 3) The strategy of switching from prasugrel to clopidogrel has not been tested. The pharmacodynamic effects of the change are not likely to be important, but the issues of logistics, as well as physician and patient acceptance, are key. For the majority of the review staff who believe more strongly that the imbalance is spurious, the exposure issue is moot, and they would not place any limitation on duration of use. I agree with the majority view on this issue.

Some have suggested a postmarketing requirement to study the tumor issue more carefully in a randomized controlled trial. This is consistent with the advice the Division received from the Division of Drug Oncology Products, Office of Oncology Drug Products, OND. The Division received advice from the Division of Epidemiology, OSE, that registry data are not likely to answer the question of cancer causality.

The Division has been in discussions with the applicant on a large outcome study (TABY), that could be used to assess the role of prasugrel in stimulating cancer. Specific areas under discussion include screening for cancer, identification of pre-existing tumors, and definitions and classification of tumors. This reviewer suggests that the completion of this study should be a post-marketing requirement under the Food and Drug Administration Amendments Act (FDAAA) of 2007, and that is the plan at this juncture.

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/s/

Ellis Unger
7/7/2009 07:06:08 PM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Date: September 29, 2008

NDA: 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets
Eli Lilly and Company

Status: priority

Submitted: 26 December 2007

Goal Date: 26 September 2008

From: Ellis F. Unger, M.D., Deputy Director, DCaRP

To: The File

Re: **Importance of Bleeding to Prasugrel's Risk Benefit Relation**

This document is based, in part, on the reviews of:

- Clinical Pharmacology and Biopharmaceutics (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Secondary (Ellis F. Unger), July 10, 2008

Overview of the Pivotal Efficacy Study, TAAL:

Study TAAL was the pivotal, active-control, double-blind, double-dummy, registrational study of prasugrel for subjects with acute coronary syndrome (ACS) who were scheduled to undergo percutaneous coronary intervention (PCI). The primary hypothesis was that prasugrel plus aspirin was superior to clopidogrel plus aspirin in the treatment of these subjects, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke (referred to as the "triple endpoint" in this document), at a median follow-up of ≥12 months.

Briefly, subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or a standard regimen of clopidogrel (300-mg load; 75 mg daily maintenance). Randomization was stratified by clinical presentation: unstable angina (UA)/ non-ST-segment elevation myocardial infarction (NSTEMI) versus ST-segment elevation myocardial infarction (STEMI). Aspirin (75-325 mg PO or 250-500-mg IV) was to be administered within 24 hours prior to the index PCI.

The intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Median length of follow-up was 450 days.

In total, 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a 1° triple endpoint event of CV death, nonfatal MI, or nonfatal stroke (Table 1). Prasugrel caused a statistically significant reduction in the triple composite endpoint in both the UA/NSTEMI and STEMI populations.

Table 1: Number and Percentage of Subjects Reaching Composite Endpoint

	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
subject population	N	n	(%)	N	n	(%)		
UA or NSTEMI	5044	469	9.3	5030	565	11.2	0.82 (0.73, 0.93)	0.002
STEMI	1769	174	9.8	1765	216	12.2	0.79 (0.65, 0.97)	0.019
Overall	6813	643	9.4	6795	781	11.5	0.81 (0.73, 0.90)	<0.001

Table 2 displays the individual components of the 1° endpoint, as well as all-cause mortality, and intracranial hemorrhage [ICH]. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group (hazard ratio [HR]=0.76; p<0.001), and this component of the composite endpoint drives the overall study results. The CV death component shows a weak trend in favor of prasugrel (HR=0.89; p=0.31). There was no effect of prasugrel on nonfatal stroke (which includes non-fatal ICH), all-cause mortality, or ICH.

Table 2: Components of 1° Efficacy Endpoint, All-Cause Death, Fatal Bleeds, and ICH

	endpoint	Prasugrel n=6813		Clopidogrel n=6795		Cox Proportional HR (95% C.I.)	p	delta events per 1000 patients treated (positive = favorable for prasugrel)
		n	%	n	%			
primary endpoint	CV Death	133	2.0	150	2.2	0.89 (0.70,1.12)	0.31	2.6
	Nonfatal MI	475	7.0	620	9.1	0.76 (0.67,0.85)	<0.001	21.5
	Nonfatal Stroke	61	0.9	60	0.9	1.02 (0.71,1.45)	0.93	-0.1
	All-Cause Death	188	2.76	197	2.90	0.95 (0.78,1.16)	0.64	1.4
	Hemorrhagic	22	0.32	5	0.07	4.39 (1.66, 11.6)	<0.002	-2.49
	Non-hemorrhagic	166	2.44	192	2.83	0.86 (0.70, 1.06)	NS	3.9
	ICH	20	0.29	19	0.28	1.05 (0.56, 1.97)	NS	-0.1

Bleeding in the Pivotal Efficacy Study, TAAL:

The risk of bleeding was well considered in the primary and secondary clinical reviewers. Prior to considering the bleeding risk associated with prasugrel in TAAL, it is useful to consider the standard Thrombosis in Myocardial Infarction (TIMI) bleeding definitions used in the study:

- TIMI Major bleeding ≡ any intracranial hemorrhage, or bleeding requiring intervention associated with a decrease in hemoglobin (Hgb) >5 g/dL;

- TIMI Minor bleeding ≡ bleeding requiring intervention that does not meet the requirements for TIMI Major bleed, and is associated with a decrease in Hgb ≥3 g/dL to ≤5 g/dL.

Table 3 summarizes the bleeding events in TAAL. Bleeding was categorized as related or unrelated to coronary artery bypass graft (CABG) surgery. Prasugrel was associated with more bleeding than clopidogrel, irrespective of the bleeding definition, seriousness, or location, and across most subgroups. (Subjects who experienced events in more than one category are represented more than once.)

Table 3: CEC Adjudicated Bleeding

Non-CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04,1.66)	0.022
TIMI Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28,1.70)	0.022

CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	213	2	0.9	224	0	0.0		
TIMI Major	213	24	11.3	224	8	3.6	3.50 (1.53,7.99)	0.002

There were 21 and 5 fatal non-CABG-related bleeding events in the prasugrel and clopidogrel groups, respectively (RR = 4.19, p=0.002; Table 3). All 5 fatal bleeding events in the clopidogrel group were intracranial in location. For the prasugrel group, 9 of 21 fatal bleeding events were intracranial, and 12 were not (5 were gastrointestinal, 2 were from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location). Given that it is generally more feasible to manage bleeding at extra-cranial sites than at intracranial sites, it is worth emphasizing that none of the deaths in the clopidogrel group, but over half the deaths in the prasugrel group, were attributed to extra-cranial sites of hemorrhage. The disparity in deaths from extracranial hemorrhage between the prasugrel and clopidogrel groups suggests that severe bleeding may be more difficult manage in patients who received prasugrel. It is noteworthy, however, that for ICH, the bleeding event least amenable to treatment, there was no difference between the two drugs. The frequencies of ICH were 19/6741 (0.28%) and 17/6716 (0.25%) in the prasugrel and clopidogrel groups, respectively.

The excess in fatal bleeding events did not lead to greater overall mortality on prasugrel; all-cause mortality slightly favored prasugrel (HR=0.95; p=0.64, Table 2). Considering actual event

rates rather than risk reduction, per 1000 patients treated with prasugrel rather than clopidogrel there are 2 additional fatal bleeding events, 3 additional non-fatal TIMI Major bleeds, 5 additional TIMI Minor bleeds, and 21 additional TIMI Minimal bleeds.

To put the bleeding into context with efficacy, compared to clopidogrel, prasugrel treatment was associated with 24 fewer endpoint events per 1000 patients treated: 21 non-fatal myocardial infarctions, 3 cardiovascular deaths, and 0 strokes. In terms of deaths therefore, prasugrel treatment (compared to clopidogrel) was associated overall with 3 fewer cardiovascular deaths per 1000 subjects treated, despite 2 additional deaths due to fatal hemorrhage. (Overall mortality favored prasugrel by 1.4 events/1000 patients treated.) Thus, prasugrel had, overall a slightly favorable effect on overall mortality or even overall mortality plus ICH, accompanied by a substantial reduction in non-fatal MIs.

Subgroups at Particular Risk of Bleeding:

There were no significant treatment-by-demographic characteristic interactions with respect to TIMI Major or Minor bleeding. None of the subgroups was associated with a particularly high HR for prasugrel, although the HR tended to be higher in females and those of lower body weight (Table 4). A few factors deserve special consideration, and they are listed below.

Table 4: Non-CABG-Related TIMI Major or Minor Bleeding Events by Subgroup

	Subject population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Overall		6741	303	4.5	6716	231	3.4	1.31 (1.11, 1.56)	0.002
Sex	female	1684	123	7.3	1798	97	5.4	1.38 (1.06, 1.80)	0.017
	male	5057	180	3.6	4918	134	2.7	1.31 (1.05, 1.64)	0.018
Age	<65	4149	141	3.4	4096	99	2.4	1.41 (1.09, 1.83)	0.008
	>=65	2592	162	6.3	2620	132	5.0	1.26 (1.00, 1.59)	0.046
	<70	5095	182	3.6	5041	138	2.7	1.31 (1.05, 1.64)	0.016
	>=70	1646	121	7.4	1675	93	5.6	1.35 (1.03, 1.76)	0.03
	<75	5850	223	3.8	5822	169	2.9	1.32 (1.08, 1.61)	0.006
	>=75	891	80	9.0	894	62	6.9	1.35 (0.97, 1.88)	0.078
Ethnicity	Caucasian	6196	281	4.5	6200	217	3.5	1.30 (1.09, 1.56)	0.003
	African	201	10	5.0	185	7	3.8	1.34 (0.51, 3.53)	0.551
	Hispanic	269	10	3.7	255	6	2.4	1.55 (0.56, 4.27)	0.393
	Asian	60	2	3.3	63	1	1.6	-	-
Weight	<50	45	2	4.4	45	6	13.3		
	50 - <70	1133	78	6.884	1232	61	4.951	1.41 (1.01, 1.96)	0.046
	70 - <90	3378	151	4.47	3297	107	3.245	1.39 (1.08, 1.78)	0.009
	>=90	2125	68	3.2	2081	55	2.643	1.22 (0.85, 1.74)	0.275

Bleeding and Advanced Age:

For the study overall, there was a striking increase in bleeding with advancing age; however, the HR for prasugrel compared to clopidogrel was consistent across all age strata. Specifically, the overall HR for bleeding was 1.31 (worse for prasugrel). Similarly, the HR was 1.35 for subjects over 70 years of age, and also 1.35 for subjects over 75 years of age. Thus, based on hazard

ratio alone, use of prasugrel, versus clopidogrel, in older patients seems to carry the same risk as in any patient, including younger patients.

However, the *outcomes* secondary to bleeding in prasugrel-treated subjects ≥ 75 years of age were of particular concern. Specifically, the frequency of fatal hemorrhage was 9/891 (1.01%) for prasugrel-treated subjects, versus 1/894 (0.11%) for clopidogrel-treated subjects. For symptomatic intracranial hemorrhage (ICH), there were 7 (0.79%) versus 3 (0.34%) cases associated with prasugrel and clopidogrel, respectively.

Moreover, prasugrel's efficacy is less certain in patients age 75 or greater. First, In TAAL, the percentages of subjects over the age of 75 experiencing a 1° endpoint event were closer for the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively) than in the overall study, where the difference was about 2%. Second, the efficacy of *clopidogrel* is less well-established in patients over the age of 75. In CURE, the registrational study of clopidogrel that compared clopidogrel and placebo in the setting of ACS, the frequencies of experiencing the triple endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke were 9.3% and 11.4% for clopidogrel and placebo, respectively. However, in subjects age 75 and over, the respective frequencies were 17.8% and 19.2%. Thus, efficacy is modest for clopidogrel in the over-75 age group, and by extension, for prasugrel.

In summary, therefore, prasugrel was associated with malignant bleeding outcomes in patients ≥75 years of age. Given that prasugrel's efficacy is less clear in this subgroup of patients, the review team opined that use of prasugrel should be discouraged in patients ≥75 years of age.

If the ≥75 year-old population is removed from TAAL, the prasugrel's bleeding risk is somewhat diminished relative to the population as a whole (Table 5). In particular, fatal bleeding events are then 12 for prasugrel vs. 4 for clopidogrel (RR=2.99); for fatal ICH and symptomatic ICH, the numbers of cases in the two treatment groups are approximately equal.

Table 5: Non-CABG-Related Bleeding in Subjects Less Than 75 Years of Age

endpoint	Prasugrel			Clopidogrel			RR (95% C.I.)
	N	n	%	N	n	%	
TIMI Fatal	5850	12	0.2	5822	4	0.1	2.99 (0.96,9.3)
TIMI Life-Threatening	5850	67	1.1	5822	45	0.8	1.48 (1.02,2.16)
TIMI Major	5850	119	2.0	5822	88	1.5	1.35 (1.02,1.77)
TIMI Minor	5850	119	2.0	5822	95	1.6	1.25 (0.95,1.63)
Fatal ICH	5850	5	0.1	5822	4	0.1	1.24 (0.33,4.63)
Symptomatic ICH	5850	12	0.2	5822	14	0.2	0.85 (0.39,1.84)

Patients with Prior History of Transient Ischemic Attack or Stroke:

The clinical outcomes were particularly poor for prasugrel-treated subjects with a prior history of transient ischemic attack (TIA) or non-hemorrhagic stroke. Because of the risk of ICH, potential

subjects with a history of hemorrhagic stroke, ischemic stroke ≤3 months prior to screening, intracranial neoplasm, arteriovenous malformation, or aneurysm were excluded from participation in TAAL. These criteria allowed entry to patients with a history of ischemic stroke >3 months prior to screening, as well as patients with a history of TIA.

For subjects with a prior history of TIA or non-hemorrhagic stroke (the latter >3 months prior to screening), a subgroup comprising 3.8% of the total study population, the HR for the composite efficacy endpoint was unfavorable for prasugrel, going against the grain of the study as a whole. The HR was 1.44 in favor of *clopidogrel*: 50 of 262 prasugrel treated subjects (19.1%) experienced an endpoint event, compared to 36 of 256 clopidogrel-treated subjects (14.4%). Of note, approximately 1/3 of the endpoint events in the prasugrel group were stroke. Specifically, 6.5% of subjects in the prasugrel treatment group experienced a stroke on study (2.3% ICH; 4.2% thrombotic) compared to 1.2% in the clopidogrel treatment group (0% ICH; 1.2% thrombotic), for a HR of 5.64 (95% C.I.: 1.65, 19.3). If stokes are subtracted from the composite endpoint, the frequencies of events are similar in the prasugrel and clopidogrel groups (12.6% and 13.2%, respectively). In patients with no prior history of TIA or non-hemorrhagic stroke, the incidence of stroke was 0.9% (0.2% ICH) in the prasugrel treatment group and 1.0% (0.3%) in the clopidogrel treatment group.

It is striking that more than one-quarter of the non-fatal stokes in the prasugrel treatment group (17 of 61) occurred in the sub-population of subjects with a history of prior TIA or non-hemorrhagic stroke, a sub-population encompassing only 3.8% of the total subject population. Moreover, it should be re-emphasized that subjects with a history of ischemic stroke within 3 months of randomization, as well as subjects with a history of hemorrhagic stroke at any time, were excluded from the study. (It is possible that such patients would have fared even worse.)

Based on these concerns, the review team recommended a contraindication in the labeling for prasugrel in patients with a prior history of TIA or stroke (hemorrhagic, non-hemorrhagic, or unknown).

Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery:

The frequency of CABG-related TIMI major bleeding was higher in subjects treated with prasugrel compared to clopidogrel. For both drugs, but especially for prasugrel, the length of time of discontinuation of the drug in advance of CABG was an important determinant of bleeding frequency. When CABG was performed within 3 days of discontinuing prasugrel, the frequency of TIMI Major or Minor bleeding was 12/45 = 27%. For clopidogrel, the corresponding frequency was 3/60 = 5%. The respective frequencies for discontinuation of prasugrel and clopidogrel >3 to ≤7 days prior to CABG were 11% and 3%, respectively. Between 7 and 14 days, the respective frequencies were 10% and 7%. Thus, for prasugrel, it is clear that a longer period of discontinuation will result in less bleeding, and that the risk of bleeding within 3 days of discontinuing prasugrel is particularly high.

Practically speaking, the increased frequency of CABG-related TIMI major bleeding with prasugrel is principally a cause for concern in the setting of urgent CABG, where there is no opportunity to stop the drug. The review team concluded that use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility. For elective CABG, it is reasonable to discontinue prasugrel 7 or more days prior to surgery.