DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

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EFFIENT™ (prasugrel hydrochloride) Tablets
Eli Lilly and Company

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To: The File

Re: **Prasugrel's Association with Cancer**

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

- Chemistry (S. Chatterjee, Z. Ge, and K. Srinivasachar), May 14, 2008
- Preclinical Pharmacology and Toxicology (B. Tesfamariam and A. DeFelice), April 26, 2008
- Clinical Pharmacology and Biopharmaceutics (E. Mishina, S. Mada, P. Marroum, R. Madabushi, Y. Wang), May 23, 2008
- Clinical (K. Hicks), April 28, 2008
- Secondary (E. Unger), July 10, 2008
- Secondary (T. Marciniak), June 19, 2008
- Consult from Division of Epidemiology, Office of Surveillance and Epidemiology (D. Wysowski), June 12, 2008
- Consult from Division of Drug Oncology Products, Office of New Drugs (B. Mann, J. Johnson, P. Cortazar)

Study TAAL[1] 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 death, nonfatal myocardial infarction, or nonfatal stroke, at a median follow-up of ≥12 months. 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). All subjects received standard therapies, including aspirin.

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.

[1] "A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38"

Prasugrel succeeded on the primary efficacy endpoint; however, its use was associated with proportionally greater numbers of cancers than clopidogrel. Depending on the particular criteria used to identify the cases, the relative risk (RR) of cancer could be as low as 1.19, or as high as 1.52.

Sponsor's Initial Analyses of Neoplasia:

The applicant highlighted the imbalance in neoplasia in their initial submission (H7T-MC-TAAL Study Report; section 12.4.4); however, their analyses were difficult to interpret. There was not always a clear distinction between neoplasms known at the time of randomization versus those discovered during the course of the study, there was little attempt to categorize neoplasms as malignant or non-malignant, and there was little emphasis on categorization of cancers by organ or organ system.

The distinction between "pre-existing" versus "new" neoplasms was particularly difficult. A "Pre-Existing Conditions" case report form (CRF) was used to record "*...all ongoing medical conditions at the time of study entry/screening.*" There appeared to be inconsistencies as to whether investigators recorded, or did not record, histories of pre-existing neoplasms, presumably related to their interpretations of whether or not a cancer was an "ongoing medical condition." For example, some investigators might consider a bladder cancer, resected 7 years prior to admission without known recurrence, as an "ongoing medical condition," whereas others might not. Moreover, for patients in the throes of an acute coronary event, it is safe to presume that there was little emphasis on recording historical information relevant to prior cancers.

For treatment-emergent serious adverse events in the system organ class (SOC) "neoplasms benign, malignant and unspecified (including cysts and polyps)," the applicant found 87 cases in the prasugrel group, versus 60 in the clopidogrel group, for a relative risk (RR) of 1.44, 95% confidence interval (CI) 1.04 to 2.00. The applicant provided exculpatory interpretations of the data for specific cancers, as follows:

Colorectal Cancer: The applicant found 19 colonic and rectal neoplasms in the prasugrel group and 8 in the clopidogrel group, but found reassurance in the fact that half of cases in the prasugrel group were discovered as a result of an antecedent GI bleed. (Because GI bleeding was more common in prasugrel subjects, they reasoned that more GI cancers would be detected.)

Breast Cancer: The applicant counted 5 cases of breast cancer in the prasugrel group, versus 1 in the clopidogrel group, but the relatively short time frame between initiation of study drug and diagnosis, for at least some of the cases, assuaged the applicant's concern.

Lung Cancer: There were 8 and 2 lung cancers reported as adverse events in the prasugrel and clopidogrel groups, respectively. However, when "lung neoplasms" were added to the cancers, the respective numbers were 12 and 10. The applicant determined, therefore, that the numbers of subjects with lung neoplasm were not different between treatment groups.

Prostate Cancer: Sixteen subjects in the prasugrel group and 9 in the clopidogrel group experienced an adverse event for prostate cancer or adenoma. The applicant took reassurance from the fact that in half of the 16 cancers in the prasugrel group, the diagnosis was made within 6 months of starting the study drug; therefore, they considered these unlikely to represent new cancers.

The applicant's summary interpretation, as stated in the original submission, was (page 899, H7T-MC-TAAL Study Report):

> "Cases of malignancy were reported at a frequency that was higher in the prasugrel than in the clopidogrel group. In some cases, such as prostate cancer, this appears to be a coincidental finding since about half of the cases were reported within 6 months of starting drug. In the case of colon cancer, they were often discovered during a diagnostic procedure following a bleed. In summary, there is no evidence that use of prasugrel is associated with a higher risk of cancer."

Further Analyses:

The applicant espoused the view that the observed difference between prasugrel and clopidogrel in the frequency of neoplasms was the result of ascertainment bias. They argued that prasugrel caused a 30-40% increase in bleeding rates relative to clopidogrel. A disproportionately greater frequency of bleeding events in the prasugrel group would lead to a disproportionately greater number of patient evaluations, which would uncover disproportionately more cancer cases.

Although the theory seemed plausible on its face, the Division undertook its own analysis of the cases, excluding cancers where a hemorrhagic adverse event preceded the cancer *in the same organ system as the cancer*, i.e., hemoptysis for lung cancer, hematuria for genitourinary cancers, gastrointestinal (GI) bleeds for GI cancers, and dysfunctional uterine bleeding for gynecologic cancers. The analysis showed that the between-group difference in neoplasms largely persisted.

The Division sought additional information from the applicant, to clarify diagnoses and malignancy status for all cases, to distinguish new from pre-existing cancers, to collect investigators' assessment of symptoms, signs, and laboratory studies that led to a diagnosis, and to collect information on vital status. The applicant developed "Neoplasia" case report forms to capture this information, and sent clinical monitors to the all sites with an affected subject to oversee collection of the data.

The applicant provided their new analyses in a May 9, 2008, submission, wherein they identified 313 subjects as having experienced an adverse event within the "Neoplasms Benign, Malignant, and Unspecified" SOC, either as: 1) a newly diagnosed adverse event, or 2) a pre-existing condition that increased in severity during the conduct of the trial. There were 175 and 138 subjects treated with prasugrel and clopidogrel, respectively, who had one or more of these events during the study. Table 1 shows the applicant's tabulation of these neoplasms, and is identical to Table 10 from the applicant's May 9, 2008 submission (except for the addition of a final line that omits non-melanomatous skin cancers).

Their analysis considered "non-benign" neoplasms, which included neoplasms known to be malignant and those whose nature was undetermined. The RR for prasugrel vs. clopidogrel was 1.19 (95% CI: 0.89, 1.58). Because non-melanomatous skin cancers are readily curable by excision and generally not serious in nature, they are often considered separately from solid tumors. When such tumors were excluded from this analysis, there were 94 and 72 new, non-benign neoplasms in the prasugrel and clopidogrel groups, respectively, for a RR of 1.30 (95% CI: 0.96, 1.76).

Table 1: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

neoplasm location	prasugrel	clopidogrel
brain	0	1
eye	0	1
oral cavity and pharynx	1	2
breast	4	1
lung and bronchus	18	14
other respiratory/thoracic	1	0
any GI site	35	25
colorectal, stomach, esophagus	31	21
colorectal	20	11
esophagus	4	3
stomach	7	7
pancreas	2	3
liver	0	1
gallbladder/biliary	2	0
any GU site	20	19
kidney	5	4
bladder	5	8
prostate	10	7
gynecologic	2	1
malignant melanoma	3	2
non-melanomatous skin	6	12
endocrine	2	0
any hematologic	4	4
leukemia	2	1
lymphoma	2	2
other hematologic	0	1
metastasis unknown primary	3	0
other unknown primary	0	1
unknown	1	1
other		
all	100	84
all, excluding non-melanomatous skin	94	72

In terms of the applicant's original contention that excess cancers were detected in the prasugrel group because of a higher incidence of bleeding events (ascertainment bias), the numbers of new, non-benign neoplasms where bleeding or anemia led to a diagnosis were 37 and 33 in the prasugrel and clopidogrel groups, respectively. Thus, the data did not support the applicant's claim of ascertainment bias; RR was largely unchanged when such cases were eliminated from the totals.

Cancer Mortality: 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 imbalance in cancer deaths is concerning, because mortality would not be expected to be affected by ascertainment bias. The applicant commented as follows:

> "The proportion of subjects diagnosed with a new nonbenign neoplasm that died due to malignancy was similar between treatment groups (27 of 100 subjects, 27% prasugrel; 19 of 84 subjects, 23% clopidogrel)."

The applicant subsequently made the argument that cancer deaths were discovered as a result of the additional data collection that preceded the May 9, 2008 submission. Specifically, they noted that vital status was obtained for 175 subjects treated with prasugrel and 138 subjects treated with clopidogrel (ratio 1.27). Therefore, given similar cancer fatality rates in two groups of different sizes, the imbalance in cancer deaths was uninterpretable.

FDA Analyses:

The Division performed an independent analyses of the cancer cases, and found some differences with the applicant with respect to whether particular cases represented neoplasia, whether neoplasms were histologically malignant, benign, or undetermined, and whether or not they had been known at screening. Some of the disagreement was related to whether particular tumors were classified as "pre-existing" if no formal diagnosis had been established prior to the adverse event. The Division also identified a small number of cases that had not been previously reported as neoplasia by the applicant.

Dr. Marciniak found 100 and 66 non-benign tumor cases in the prasugrel and clopidogrel groups, respectively (excluding non-melanomatous skin cancers), for a RR of 1.51, 95% confidence interval (CI) 1.11-2.06. Figure 1 shows the Kaplan-Meier time-to-event analysis as presented in prasugrel's CDER Regulatory Briefing on 9/5/2008, where the log-rank p=0.009. The applicant found 6 and 12 cases of non-melanomatous skin cancer in the prasugrel and clopidogrel groups, respectively. If these cases had been included in the Marciniak analysis, the RR would have been 1.35 (95% CI 1.01-1.81).

Figure 1: New, Non-Benign Neoplasms – DCaRP Analysis

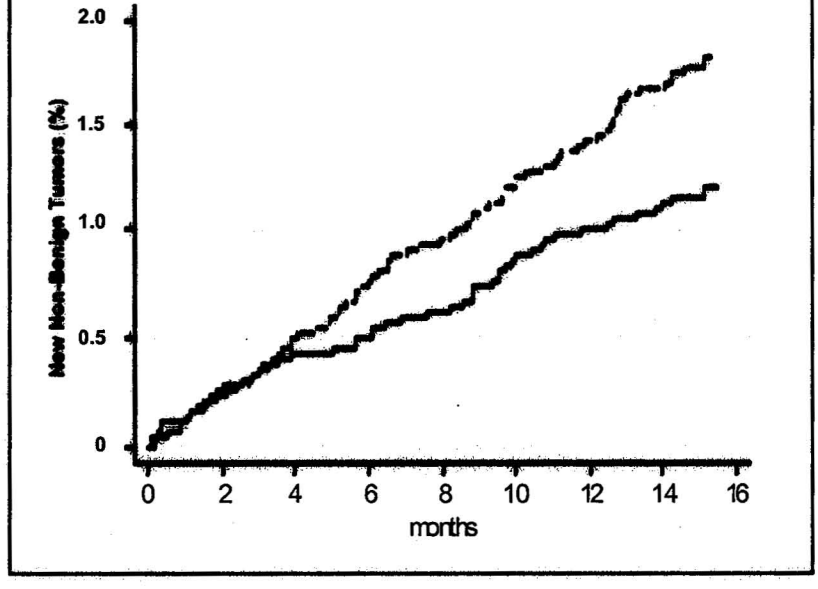

Table 2 summarizes the results of analyses conducted by the applicant and initial analyses by Dr. Marciniak.

Table 2: Relative and Absolute Risk of Non-Benign Neoplasia; Analyses by Sponsor and Marciniak

Analysis by:	Prasugrel n=6741		Clopidogrel n=6716		Relative Risk (95% CI)	Absolute Risk (%)
	n	%	n	%		
Sponsor (5/9/08)						
all non-benign	100	1.48	84	1.25	1.19 (0.89, 1.58)	0.23
exclude skin	94	1.39	72	1.07	1.30 (0.96, 1.76)	0.32
Marciniak						
all non-benign	106	1.57	78	1.16	1.35 (1.01, 1.81)	0.41
exclude skin	100	1.48	66	0.98	1.51 (1.11, 2.06)	0.50

Because of the disparity between the accounting of the cases by Dr. Marciniak and the applicant, much additional attention was given to obtaining agreement on the actual numbers of cases of new, non-benign neoplasms. Doctors Marciniak, Unger, Stockbridge, and Temple blindly adjudicated a subset of the cases, and conclusions were shared with the applicant. Agreement was reached that the numbers of cases of new, non-benign neoplasms were 94 and 80 in the prasugrel and clopidogrel groups, respectively. Subsequently, however, Dr. Marciniak argued successfully that two cases should be added to the prasugrel group, and two subtracted from the clopidogrel group, making the totals 96 and 78 in the prasugrel and clopidogrel groups, respectively. Still later, Dr. Marciniak indentified 7 additional subjects who had experienced adverse events that were unquestionably classified as skin carcinomas (basal cell or squamous cell), but had not been considered in any of the applicant's analyses because they had not been coded to the system organ class "neoplasms benign, malignant and unspecified (including cysts and polyps)" in the original submission. Six of these subjects were in the prasugrel group, and one was in the clopidogrel group. Thus, in the Division's final accounting, the numbers of new, non-benign neoplasms were 102/6741 (1.51%) in the prasugrel group and 79/6716 (1.18%) in the clopidogrel group, for a relative risk of 1.29 (95% C.I. 0.96-1.72).

Given that prasugrel and clopidogrel share a number of similarities in their mechanisms of action, Dr. Marciniak re-visited the large clopidogrel outcome trials, CAPRIE, CREDO, CURE, and CHARISMA, with a combined sample size of over 39,000 subjects. He found no consistent trends suggesting that clopidogrel is a cancer promoter. There were a few differences in frequencies of particular tumor types in some of the studies, but the results were inconsistent. CURE showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 versus 8), but this was not observed in CAPRIE or CHARISMA. Clopidogrel was associated with excess lung cancer in CURE (12 versus 7) and CREDO (5 versus 0), but not in the larger CAPRIE (72 versus 74) or CHARISMA Studies (70 versus 63). Moreover, Dr. Marciniak suggested that the lack of a consistent trend indirectly undermines the applicant's assertion that excess bleeding led to ascertainment bias in TAAL, given that bleeding would have been expected to lead to ascertainment bias in the clopidogrel development program, yet no signal was found.

The Division sought the expertise of the Division of Drug Oncology Products, and their consult team highlighted the following points (paraphrased here):

1. In terms of supporting the concept that prasugrel causes cancer, no analyses based on TAAL can be conclusive:

a. TAAL was not designed to compare the cancer incidences between study arms, so the Type I error rate for this exploratory significance testing is essentially unknown.

b. The absence of cancer at entry was not a requirement. There was no baseline cancer screening evaluation of study subjects.

c. The clinical significance of the statistical findings obtained by combining of different cancers in the comparisons is hard to interpret given differing etiologies and natural histories of the diverse types of cancers.

2. There are no data in TAAL to support a belief that prasugrel is a "promoter" in humans. Given the absence of a well defined cancer screening at study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study are more likely to be incidental.

3. To determine whether worsening of cancer was related to study drugs or was spontaneous, one would need to study the progress of known cancers when exposed to study drugs and a placebo to address this issue. Such trials are not possible in humans for clinical, statistical, and ethical reasons.

4. Epidemiologic comparison with the SEER data may be helpful; however, the results are of limited value and likely to be inconclusive as the study population in TAAL is drawn from several different countries. SEER data come from US populations from selected cities/regions.

5. A definitive study would require a screened population (cancer free) of adequate size, randomly assigned to the study treatments and followed up for adequate time.

Non-Clinical Data:

In considering the plausibility of prasugrel-induced carcinogenesis or tumor promotion, there are few data in the literature to support a mechanism. Specifically, there is little evidence suggesting that prasugrel, clopidogrel, or modulation of the $P2Y_{12}$ receptor would have important effects on genotoxicity, tumorigenesis, tumor promotion, metastasis, or angiogenesis.

The 2-year rodent carcinogenicity studies were described fully in the Preclinical Pharmacology and Toxicology review. The rodent data do not show significantly increased rates of malignant neoplasms, although positive trends in some tumor types were highlighted by Dr. Marciniak. The two-year rat carcinogenicity study showed findings primarily consistent with hepatic enzyme induction. At doses in the mouse approximating 500 times the exposure in humans, there was a statistically significant dose-response relationship for hepatocellular adenoma. There was also a non-statistically significant trend in favor of increased hepatocellular carcinomas at the highest dose (300 mg/kg/day). Prasugrel was not associated with greater numbers of malignant tumors in extra-hepatic tissues. The Pharmacology/Toxicology review team and the Executive Carcinogenicity Advisory Committee opined that they found no evidence of a prasugrel-associated increase in malignant tumors in either species, and interpreted the results as reassuring.

Considering the brevity of the clinical trial TAAL relative to the typical doubling time of common tumors, there was uniform agreement within the review team that if, in fact, prasugrel was causally related to the imbalance in neoplasms, the mechanism must have involved tumor promotion rather than carcinogenicity. On October 17, 2008, the Division asked the applicant to conduct tumor progression studies to evaluate the effects of prasugrel metabolites *in vitro*, using