

February 19, 2009

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Building 51, 6th Floor
Silver Spring, MD 20993

Dear Dr. Woodcock,

The Cardiovascular and Renal Drugs Advisory Committee met on February 3, 2009 to discuss New Drug Application 22-307, prasugrel hydrochloride for use in acute coronary syndrome (ACS). Based on a review of the briefing materials prepared for this meeting, we have several concerns about the efficacy and safety of this drug, and urge you to require the company to clearly communicate the drug's risks in the product labeling. We recommend including a boxed warning in the labeling that describes the lack of efficacy of prasugrel in patients with prior stroke or TIA, and the substantial risk of hemorrhage in certain patient groups. Also, patients taking prasugrel should be given a Medication Guide that clearly explains these risks, and a post-marketing study should be conducted to evaluate whether or not prasugrel increases the risk of cancer, as found in the randomized controlled clinical trial submitted by the company..

In addition, we have concerns about the Advisory Committee meeting itself. In particular, we believe that the absence of any members of the Drug Safety and Risk Management Advisory Committee and the last-minute removal of Dr. Sanjay Kaul, a regular voting member of the Cardiovascular and Renal Drugs Advisory Committee with substantial knowledge about prasugrel, significantly limited critical discussion of the safety of this drug.

I) EFFICACY

The efficacy claim for use of prasugrel in ACS is based on TRITON-TIMI 38, a multicenter, randomized controlled trial that compared prasugrel with clopidogrel in 13,619 patients with ACS and plans to undergo immediate percutaneous coronary intervention. The primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke, occurred in 9.3% of patients on prasugrel and 11.2% of patients on clopidogrel (HR 0.81, 95% CI 0.73-0.90).¹

Nonfatal MI accounted for the majority of primary endpoints (74% for prasugrel, 80% for clopidogrel). The majority of nonfatal MIs (60%) were periprocedural (occurring < 24 hours after PCI), most of which were asymptomatic elevations in cardiac enzymes. The hazard ratio for cardiovascular death trended towards benefit for prasugrel but was nonsignificant (HR 0.89, 95%

¹ HR = hazard ratio, CI = confidence interval

CI 0.70-1.12). For nonfatal stroke, prasugrel was slightly but nonsignificantly worse (HR 1.02, 95% CI 0.71-1.45).

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	10074	182	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	3534	101	2.9	0.74 (0.50,1.09)	0.129
	All ACS	6813	133	2.0	6795	150	2.2	13608	283	2.1	0.89 (0.70,1.12)	0.307
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	10074	821	8.1	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	3534	274	7.8	0.75 (0.59,0.95)	0.016
	All ACS	6813	475	7.0	6795	620	9.1	13608	1095	8.0	0.76 (0.67,0.85)	<0.001
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	10074	81	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	3534	40	1.1	1.10 (0.59,2.04)	0.77
	All ACS	6813	61	0.9	6795	60	0.9	13608	121	0.9	1.02 (0.71,1.45)	0.93

Components of Primary Efficacy Endpoint. Table 7 from Secondary Review of prasugrel (NDA 22-307) by Ellis Unger, M.D., dated January 9, 2009.

Time Interval	Nonfatal MI Not Associated with Stent Thrombosis		Nonfatal MI Associated with Stent Thrombosis	
	Clopidogrel N ^a (%) ^b	Prasugrel N ^a (%) ^b	Clopidogrel N ^a (%) ^b	Prasugrel N ^a (%) ^b
≤ 24 hours	308 (58.2%)	266 (61.6%)	19 (20.9%)	13 (28.6%)
> 24 hours – 30 days	48 (9.1%)	34 (7.9%)	47 (51.6%)	5 (11.9%)
> 30 days to 1 year	154 (29.1%)	119 (27.5%)	19 (20.9%)	22 (52.4%)
> 1 year	16 (3.0%)	10 (2.3%)	6 (6.6%)	3 (7.1%)
Unknown	3 (0.6%)	3 (0.7%)	0	0
Total	529	432	91	43

^aN=Number of subjects experiencing the indicated event.
^b%=N divided by the column total.

Summary of Nonfatal Myocardial Infarction. Table 11 from Clinical Review of prasugrel (NDA 22-307) by Karen Hicks, M.D., dated April 28, 2008.

Although periprocedural elevations in cardiac enzymes are thought to have some prognostic significance, they are probably less clinically relevant than symptomatic myocardial infarctions, and certainly less relevant than cardiovascular death. Thus, any assessment of the benefits and risks of prasugrel versus clopidogrel must include the consideration that much of the treatment effect for prasugrel is driven by a decrease in asymptomatic elevations in cardiac enzymes.

In some subgroups, efficacy appeared reduced or absent. For patients over the age of 75, the reduction in the primary endpoint with prasugrel was small and nonsignificant (HR 0.94, 95% CI 0.75-1.18). Patients with a prior history of stroke or transient ischemic attack (TIA) experienced an *increase* in the primary endpoint with prasugrel (HR 1.38, 95% CI 0.89-2.13). The composite event rate in this subgroup was much higher overall (17.9% with prasugrel, 13.7% with clopidogrel), and the increase in risk of subsequent stroke was particularly high (6.5% for prasugrel vs 1.2% for clopidogrel, HR 5.64, 95% CI 1.65-19.3).

Endpoint	Prior TIA or Stroke?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Triple Composite	Yes	262	47	17.9	256	35	13.7	1.38 (0.89, 2.13)	0.15
	No	6551	596	9.1	6539	746	11.4	0.79 (0.71, 0.88)	
CV Death	Yes	262	9	3.4	256	15	5.9	0.63 (0.28, 1.44)	0.27
	No	6551	124	1.9	6539	135	2.1	0.92 (0.72, 1.17)	
Nonfatal MI	Yes	262	29	11.1	256	25	9.8	1.15 (0.67, 1.97)	0.61
	No	6551	446	6.8	6539	595	9.1	0.74 (0.66, 0.84)	
Nonfatal Stroke	Yes	262	15	5.7	256	2	0.8	7.39 (1.69, 32.3)	0.002
	No	6551	46	0.7	6539	58	0.9	0.79 (0.54, 1.17)	
All Stroke	Yes	262	17	6.5	256	3	1.2	5.64 (1.65, 19.3)	0.002
	No	6551	58	0.9	6539	68	1.0	0.85 (0.60, 1.21)	

Outcomes in Patients With and Without a Prior History of Stroke or TIA. Table 8 from Secondary Review of prasugrel (NDA 22-307) by Ellis Unger, M.D., dated January 9, 2009.

II) SAFETY: Hemorrhage

The most serious safety issue with prasugrel is the significantly increased risk of hemorrhage when compared to clopidogrel (28.6% versus 21.0%), a drug that itself presents a hemorrhage risk in comparison to placebo. TIMI life-threatening bleeding not related to coronary artery bypass graft surgery (CABG) was increased 52% (HR 1.52, 95% CI 1.08-2.13).² Twenty-one non-CABG-related fatal bleeding events occurred with prasugrel compared to five with clopidogrel (HR 4.19, 95% CI 1.58-11.1).

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	

Non-CABG-Related Bleeding Events. Taken from Table 11 from Secondary Review of prasugrel (NDA 22-307) by Ellis Unger, M.D., dated January 9, 2009.

The magnitude of the increased bleeding risk for patients over the age of 75 (HR 1.35) was similar to that for patients below the age of 75 (HR 1.32). However, the outcomes were far more severe. In the subgroup of patients over the age of 75, fatal hemorrhage occurred in 1.0% of patients on prasugrel compared to only 0.1% of patients on clopidogrel.

² TIMI life-threatening bleeding is defined as bleeding that is fatal, leads to hypotension requiring treatment with intravenous inotropic agents, requires surgical intervention for ongoing bleeding, requires transfusion of 4 or more units of blood over a 48 hour period, or is a symptomatic intracranial hemorrhage.

The bleeding risk in patients undergoing CABG was “particularly malignant,” in the words of Dr. Ellis Unger, M.D., Deputy Director of the Division of Cardiovascular and Renal Products. TIMI major bleeding events occurred in 11.3 % of patients on prasugrel, of which 2 were fatal, compared to just 3.6% of patients on clopidogrel.³

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	

CABG-Related Bleeding Events. Taken from Table 11 from Secondary Review of prasugrel (NDA 22-307) by Ellis Unger, M.D., dated January 9, 2009.

III) SAFETY: Cancer

Also of concern is the increased rate of new cancers and cancer deaths seen in patients on prasugrel. Based on the sponsor’s classification of neoplasms, the rate of new cancers with prasugrel was greater than with clopidogrel (1.82% vs 1.54%, RR 1.18, p = 0.28).⁴ The relative risk increased to 1.31 if non-melanomatous skin cancers were excluded (p = 0.09). Cancer deaths were also more likely: 33 occurred with prasugrel and 21 with clopidogrel (RR 1.57, 95% CI 0.91-9.71).

³ TIMI major bleeding is defined as bleeding that is intracranial, clinically overt, or results in a drop in hemoglobin of 5 g/dL or greater.

⁴ RR = relative risk

neoplasm location	prasugrel	clopidogrel	
	n=6741	n=6716	
brain	0	1	
endocrine	1	0	
oral cavity and pharynx	1	2	
breast	3	1	
lung and bronchus	16	12	
other respiratory/thoracic	1	0	
any GI site	34	24	
colorectal, stomach, esophagus	30	20	
colorectal	19	10	
esophagus	4	3	
stomach	7	7	
pancreas	2	3	
liver	0	1	
gallbladder/biliary	2	0	
any GU site	19	20	
kidney	6	3	
bladder	5	8	
prostate	8	9	
gynecologic	2	1	
malignant melanoma	3	2	
non-melanomatous skin	6	13	
endocrine	1	0	
any hematologic	3	3	
leukemia	1	1	
lymphoma	2	1	
other hematologic	0	1	
metastasis unknown primary	2	0	
other unknown primary	0	1	
unknown	2	0	
all	94	80	RR = 1.18
all, excluding non-melanomatous skin	88	67	RR = 1.31

New Non-benign Neoplasms. Table 21 from Secondary Review of prasugrel (NDA 22-307) by Ellis Unger, M.D., dated January 9, 2009.

An independent analysis performed by Medical Team Leader Dr. Thomas Marciniak, excluding non-melanomatous skin cancers, found an increased risk of new solid cancers with prasugrel compared to clopidogrel (RR 1.41, $p = 0.02$). The relative risk increased to 1.62 if pre-existing cancers that worsened were included in his analysis ($p = 0.001$).

We agree with the FDA reviewers that ascertainment bias cannot account for the observed increase in cancer rates with prasugrel, because the rate was similarly increased in patients with and without bleeding or anemia, and cancer deaths were also increased in patients taking prasugrel. As suggested by the FDA reviewers, it is plausible that prasugrel increases cancer rates by acting as a promoter through its potent antithrombotic effect, rather than as a carcinogen. Whether or not nonmelanomatous skin cancers or worsening cancers are included in the tally, the increase in cancer and cancer death rates with prasugrel is a concerning safety signal that requires appropriate labeling and further study.

IV) ADVISORY COMMITTEE MEETING

The February 3, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee took place in a “family picnic” atmosphere, as described by one participant. There was little critical discussion of the relative importance of asymptomatic myocardial infarction as an outcome, or of the safety risks of prasugrel. The committee voted unanimously in favor of approval of prasugrel and recommended only mild warnings about bleeding and possible cancer risks. Specifically, the committee recommended against limiting prasugrel use in patients over the age of 75, despite minimal benefit and an increased risk of fatal bleeding. Several members proposed a dose reduction from 10mg to 5mg to mitigate the bleeding risk in patients over the age of 75 or weighing less than 60kg, despite the complete absence of any clinical outcomes data to support the use of this dose. Also, data on the increased rate of cancer and cancer deaths with prasugrel was trivialized and relegated to the “Adverse Events” portion of the label. Some members favored excluding this information from the label completely.

Given the list of questions presented to the Advisory Committee by the FDA, it seems fair to assume that the meeting was held primarily to provide guidance on the safety issues surrounding prasugrel. Therefore, we were surprised to learn that no members of the Drug Safety and Risk Management Advisory Committee were invited to participate. Even more conspicuous was the absence of Dr. Sanjay Kaul, a cardiologist and regular voting member of the Cardiovascular and Renal Drugs Advisory Committee, who was removed immediately before the meeting without explanation.

Dr. Kaul is a prominent researcher who is known for his critical analysis of the results of several large clinical trials. After the results of TRITON-TIMI 38 were published in *The New England Journal of Medicine* in 2007, he raised concerns about the overall bleeding risk with prasugrel and use of the drug in patients prior to defining coronary anatomy. At the American Heart Association meeting in November 2008, Dr. Kaul presented several analyses of TRITON-TIMI 38, questioning the clinical significance of some of the efficacy findings and the impact of excluding high-risk subgroups on the overall risk-benefit profile of prasugrel.

According to Dr. John Jenkins, director of the FDA Office of New Drugs, FDA staff learned about the abstracts presented at the AHA meeting last year and raised the question of a possible “intellectual bias.” The term bias implies a preference for a particular interpretation of the data that lacks objectivity and is based on peripheral concerns. It is unclear how the conclusions Dr. Kaul came to regarding the efficacy and safety of prasugrel suggest any bias, as opposed to well-reasoned scientific inquiry. On the contrary, he is free from any financial conflicts of interest, which are not uncommon on FDA Advisory Committees and for which the FDA has an explicit policy to manage.

The last-minute removal of Dr. Kaul from the Advisory Committee meeting severely undermined the credibility of the meeting and has been widely criticized for several reasons. First, the discussion appeared one-sided and weighted against the significance of the safety risks of prasugrel. Dr. Kaul was perhaps the Advisory Committee member best-positioned to contribute to a much-needed critical discussion, given that his analysis of the results of TRITON-TIMI 38 addressed many of the very questions presented to the Advisory Committee by the FDA. Second, the decision to remove Dr. Kaul was made behind closed doors and lacked transparency. Finally, the removal of the only Advisory Committee member to seriously question

the efficacy and safety of prasugrel suggests that the outcome of the meeting was pre-determined, and that the motivation for Dr. Kaul's removal was to silence a critical view of the drug.

V) REGULATORY ACTION

The decision of whether or not to approve prasugrel for use in ACS must be made by weighing the benefits and risks of the drug. TRITON-TIMI 38 showed that prasugrel reduces the rate of nonfatal MI, but most of these events were periprocedural and likely asymptomatic. A reduction in cardiovascular death was not clearly demonstrated.

On the other hand, prasugrel is associated with a substantial risk of hemorrhage. Although present throughout the population studied, the risk is greatest in certain subgroups. In addition, a concerning safety signal for malignancy was observed.

Dr. Unger has summarized these results quantitatively. Based on point estimates, for every 1000 patients treated with prasugrel instead of clopidogrel 21 nonfatal MIs and 3 cardiovascular deaths are prevented. In addition, 3 nonfatal TIMI Major bleeding events and 2 bleeding deaths are caused. If the FDA decides that this risk-benefit profile is favorable and approves prasugrel, a number of restrictions and warnings must be made clear in the labeling:

- 1) Prasugrel must be absolutely contraindicated in patients with a history of prior stroke or TIA. A clear increase in events (by 38%), especially subsequent strokes, was observed with prasugrel in this subgroup.
- 2) Prasugrel should not be used in patients over the age of 75, given minimal efficacy and worse bleeding outcomes in this age group.
- 3) Given the dramatically increased risk of serious bleeding after CABG, prasugrel should not be given prior to defining coronary anatomy, as some patients may require urgent bypass surgery. For patients taking the drug who proceed to CABG, it should be discontinued 7 days prior to surgery.

The above three points should be displayed prominently in a boxed warning, given that the use of prasugrel in these patient groups is likely to result in serious harm or death.

An FDA-approved Medication Guide that clearly explains the serious bleeding risk with prasugrel and its possible role in cancer promotion should be given to patients. Although the decision to initiate therapy with prasugrel will be made primarily by physicians in the setting of medical emergency, patients should be made aware of the risks associated the use of this drug, which will affect any decision on duration of therapy.

A Communication Plan to healthcare providers should be implemented that emphasizes appropriate patient selection and describes the bleeding and possible cancer risks with prasugrel.

To further elucidate the relationship between prasugrel and malignancy, a post-marketing study should be conducted that carefully collects data on pre-existing cancers at baseline and new cancers and cancer mortality on follow up. This study should be powered to exclude at least a twofold increase in cancer risk over a period of several years. These measures can be incorporated into any planned clinical trials, rather than mandating a separate study.

Finally, the public still awaits an adequate explanation for the abrupt removal of Dr. Sanjay Kaul from the Advisory Committee meeting on February 3rd. Now, more than ever, the FDA needs to clarify and disclose to the public how it defines “intellectual bias” and the policy and procedures by which it decides to exclude members of Advisory Committees based on such perceived bias. The case of Dr. Kaul creates the appearance of a lack of such a policy, or the flawed execution of one if it exists.

Sincerely,

James Floyd, M.D.
Researcher

Sidney Wolfe, M.D.
Director

Public Citizen, Health Research Group

cc: Frank Torti, M.D., M.P.H., Acting Commissioner, FDA
Randall Lutter, Ph.D., Deputy Commissioner for Policy, Planning & Preparedness,
Office of the Commissioner