

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

DIVISION DIRECTOR MEMO



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22-307 (Effient¹; prasugrel for PCI-managed STEMI and ACS)

Sponsor: Lilly

Review date: 25 April 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

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HFD-110/Pease-Fye/Unger

This memo conveys the Division's recommendation to approve prasugrel for STEMI and unstable angina or NSTEMI. Prasugrel is a thienopyridine and it irreversibly blocks ADP-dependent platelet aggregation.

The application is well summarized in Dr. Unger's CDTL memo (10 July 2008). I summarize only the major issues.

1. Prasugrel's active metabolite is formed by serum esterases and it appears therefore to be less vulnerable to genetically mediated variability in response than is clopidogrel. However, Dr. Madabushi points out another probably equally important factor in limiting variability in response, at least to the loading dose. Prasugrel's 60-mg loading dose places plasma levels of the active metabolite high enough that the response is near E_{max} of about 80% inhibition. Variation in plasma levels will therefore have relatively small effects on response. Clopidogrel's 300-mg loading dose produces active metabolite levels near the IC₅₀, i.e., the steepest part of the exposure-response relationship, so the same proportionally sized effects on exposure will have much larger effects on response to clopidogrel.
2. A substantial fraction of the population has genetically impaired CYP 2C19 metabolism, so they produce little or no active metabolite of clopidogrel. Prasugrel has redundant metabolic pathways to generate its active metabolite. What fraction of the difference in effects of prasugrel and clopidogrel are attributable to degree of platelet inhibition (dose) or to proportion of the population able to form the active metabolite is unknown.
3. Probably the most important issue for approval is whether the incremental risk from bleeding is more important than is the incremental benefit in reducing what were a mix of subclinical and clinical myocardial infarctions. I believe the MI definition in TRITON was reasonable, and that, unlike non-fatal, non-intracranial hemorrhages, these MIs have long-term clinical impact, leading incrementally to heart failure, albeit not within the duration of TRITON.

In addition, I note that, prasugrel's benefits were across the full range of biomarker-based to clinically manifest MIs.

4. Late in development it was discovered that the hydrochloride salt of prasugrel (developed to enhance bioavailability at high gastric pH) was being back-converted to base through (b) (4). This reaction was happening in-process and during storage. Batches used in the major study probably varied widely in salt-

¹ Originally proposed name of (b) (4) appears in reviews

base ratio. In addition, widespread use of proton pump inhibitors probably blunted the advantages of the salt in many subjects. Both effects were mostly on C_{max}, which, considering the irreversible nature of thienopyridines' platelet inhibition, I would have expected to be the critical exposure parameter. However, the sponsor maintains, and our clinical pharmacology review does not refute, that AUC is better related to platelet inhibition, and, because of targeting exposure to achieve a high degree of inhibition, the variation in salt-base thus produced only a modest variability in response, estimated at about 10%. Although one can question the appearance of a poorly controlled aspect of manufacture, the drug offers a clinically important advantage over clopidogrel and the to-be-marketed formulation will have at least somewhat less variability than did the batches used in the TRITON study, and approval ought not be withheld (b) (4)

5. The foregoing would suggest that other factors affecting exposure would have little consequence on the effects of platelet inhibition. However, that does not seem to be the case. Low body weight increased the risk of bleeding. What to do to optimize net clinical benefit in such cases is unclear. Small (and therefore difficult to discern) increments in reductions in stroke or MI could offset large (and therefore relatively easy to detect) increments in bleeding risk. I favor making this choice clear to prescribers, for I see no way give very compelling advice.
6. In TAAL, prasugrel was superior to clopidogrel on the primary end point of CV death, MI, and stroke. This is the end point on which clopidogrel was shown to be superior to placebo, and clopidogrel's resulting claim encompasses all components of the composite, so there is some justification to the position that the effect of prasugrel is assured on all components, too. However, clopidogrel's claim for an effect on stroke is tenuous. In CURE (patients with ACS or NQWMI), the stroke rates were 1.2% on clopidogrel and 1.4% on placebo, a non-significant difference of 12 events. In the post-MI trial COMMIT, non-fatal stroke rates were 0.6% on both clopidogrel and placebo. I conclude that one does not know enough to conclude any effect of prasugrel on stroke in either setting.
7. In TAAL, prasugrel was superior to clopidogrel in both the STEMI and UA/NSTEMI cohorts. These two findings support one another, if that were necessary, but the overall result scarcely merits mention in labeling. The two populations are distinguishable prior to the initiation of dosing, so the overall results, largely an accident of the mix of patients in TAAL, have no relevance to anyone.
8. The advantage of prasugrel on the primary endpoint amounts to about 7.5 events prevented per 1000 patient-days on day 1 in the STEMI group, and to about 7.2 events prevented per 1000 patient-days on day 1 in the UA/NSTEMI group. Within a few weeks, the difference between treatment groups is indistinguishable from zero for STEMI patients and settles to about 0.04 events per 1000 patient-days (or about 15 events per 1000 patient-years) in the UA/NSTEMI group. Background rates (i.e., rates on placebo) drop precipitously over the same time frame, as seen in placebo groups of CURE and COMMIT.
9. The overall risk of having a serious hemorrhage is pretty small (about 4% per year on clopidogrel or 5.5% on prasugrel²). In the first two days of treatment, prasugrel causes more bleeding than clopidogrel, by about 2 events per 1000 patient-days, probably a reflection of the marked early difference in platelet aggregation. Once both drugs are at steady-state, the risk of a first serious hemorrhage is pretty constant on either treatment, higher on prasugrel by about 1.2 events per 1000 patient-days, probably a reflection of the higher steady-state platelet inhibition achieved with the prasugrel regimen.

² Based upon time to first event of non-CABG-related, TIMI Major or Minor bleeding events.

10. Thus, there is a steep reduction in risk of CV death, MI, and stroke in the weeks after STEMI and UA/NSTEMI, regardless of treatment, making any relative risk reduction less valuable as time goes on. The risk from serious hemorrhage also abates with time from a vascular intervention (or other wound), so the effect on net clinical benefit over time—for both drugs and for the difference between them—is hard to estimate. Whether there is a point at which treatment should be terminated or made less aggressive cannot be ascertained from these data, because such determination depends greatly on the clinical importance attached to various events and because of the assumptions one must make about the persistence of the effects of interventions.
11. It is natural to have difficulty putting together the increased risk of bleeding and the decreased risk of MI. Bleeding evokes a visceral response from us. Second, when the bleed happens, the physician knows he caused it by his antiplatelet (or antithrombotic) therapy, but one is much less certain that the particular patient got the benefit of treatment when the patient has no cardiovascular event on therapy. And third, we know that people who do bleed do not do well generally.

Almost without exception, development programs I see for prevention of cardiovascular events are presented with the expressed goal of minimizing risk of bleeding and then establishing minimum effectiveness either by beating a placebo or showing non-excessive loss of the apparent effectiveness of a positive control.

Lilly deserves a lot of credit for boldly targeting a higher degree of platelet inhibition than one gets with clopidogrel and targeting superiority in cardiovascular events. The trial did not leave us guessing about the long-term consequences of excess hemorrhages produced by prasugrel. The deaths, intracranial bleeds, and MIs that might have been attributable to severe bleeding were captured in the data. The only other implication of a serious bleed was the hospitalization incurred; there were no hidden costs. Death (obviously), MI (even ones unaccompanied by chest pain), and stroke, on the other hand, carry long-term consequences in loss of function and increased risk of subsequent cardiovascular events. Thus, however scary bleeding may be, a survived bleeding event is much less clinically important than is a survived MI or stroke. (And there were fewer excess “major” bleeds than there were MIs prevented on prasugrel compared with clopidogrel.) These results strongly suggest that the optimum clinical outcome from use of these agents (in most patients—see caveats below) might well lie at *higher* degrees of platelet inhibition than have yet been explored in outcome studies—if such is possible. An important goal of labeling ought to be to educate physicians about this tradeoff.

12. Patients who had an MI in study (whether or not they had one that got them into the study) did much better subsequently if they were in the prasugrel group than if they were in the clopidogrel group. Although of course this is not a randomized group at this point, it plausibly reflects the same benefit seen in subjects who entered the trial with an MI.
13. The factor most clearly identified as being disadvantageous for being randomized to prasugrel was prior TIA or stroke.

Table 1 Risk of subsequent stroke or intracranial hemorrhage among patients with prior history of TIA or stroke in TAAL.

	Pras	Clop
Stroke	6.3%	1.2%
ICH	2.3%	0

Since most of the MIs were small ones, any advantage in MI reduction on prasugrel applicable to such subjects would seem to be outweighed by the increased risk of a subsequent stroke. Prasugrel (this regimen, at least) is not preferable to clopidogrel (this regimen) in patients with prior TIA or stroke.

Patients who had a stroke during the study did poorer if they were on prasugrel than if they were on clopidogrel. Again, this is not a randomized group, but it reinforces the impression

that people who had a stroke or TIA, remotely or on therapy, cease to be good candidates for aggressive antiplatelet therapy.

14. One can make not quite as good a case to contraindicate prasugrel in elderly patients. Patients over the age of 75 in CURE (clopidogrel in ACS) had less benefit and more bleeding risk, but, in COMMIT (clopidogrel post-MI), the benefit was not different in patients over age 70. That labeling does not warn or restrict by age, and, considering the limited subset, clopidogrel use is probably warranted in both settings.

In TRITON, primary end point events were not statistically significantly different on clopidogrel and prasugrel among subjects over age 75, but the trend is favorable for prasugrel in both UA/NSTEMI (-0.4%) and STEMI (-2.6%). In STEMI, the absolute difference between arms is similar in the age <75 and >75 groups. You cannot ask for much more than that in a subset that comprises less than 15% of the total population. ICH is more common in both treatment groups among patients of age >75, but the rate is low (<1%) and the difference between prasugrel and clopidogrel is 0.45%. Thus, one gets just about the same risk reduction for cardiovascular events and increase in risk for ICH for UA/NSTEMI, and the net benefit in STEMI is more favorable—2.6% reduction in absolute risk of primary end point events or about 5 MIs prevented per ICH.

Confidence limits around these estimates are large, so I feel distinctly less compelled to give advice in labeling, but the basis for making an informed decision should be in the label, in some form. However, one could also defend a preference for clopidogrel or a contraindication in STEMI or both settings.

15. The sponsor found a nearly 50% reduction in both populations for the risk of stent thrombosis. I have no concern about the potential bias in ascertainment, but I share some of Dr. Hicks's concerns about the characterization of the events. Assessment for stent thrombosis was triggered by clinical presentation and not by routine follow-up, so there is a reasonable chance that the events in question are bona fide stent thromboses of apparent clinical significance. I supported the plan to have the sponsor perform a more conventional adjudication procedure on a subset of purported stent thrombosis cases, and I am sufficiently comforted by the results obtained that I favor incorporation of the stent thrombosis claim.
16. The sponsor's other secondary end points are generally not very informative. They include the primary end point assessed at different times or add less important and less common components to a composite end point driven largely by MI.
17. The cancer data were thoroughly discussed at the Advisory Committee meeting. I concur with their recommendation that this merits minor mention in the label's Adverse Reactions section only.

There is discussion of making collection of cancer data a PMR for the ongoing outcome study of prasugrel in medically managed ACS. The sponsor has incorporated reasonable data collection, and I do not see how making this a PMR is useful, since we cannot expect them to continue the study for this purpose if there is any other reason to abort it.

18. Thienopyridines' effects on platelet inhibition last the lifetime of the platelet, a week or more. Discontinuing treatment for a day or so will have no effect on one's ability to manage a bleeding episode. When it is appropriate to reverse inhibition, say, for surgery, one should be able to wait a day or so from the last dose (thus, several PK half-lives), and then administer fresh platelets. I know of no empirical data to test this. Collecting such data is a reasonable, feasible, and useful PMR.
19. I have some reservations about the box warning on bleeding as it has the potential to dissuade use. I favor wording that is geared toward ensuring people remain on or return to therapy after hemorrhage, as subsequent MI is a greater risk than is clinically important bleeding.

20. The same rationale supports a medication guide. Patients should be told that there is a (still pretty small) risk that they will have a serious hemorrhage that will require medical attention to manage, but that it is important that they continue dosing.
21. Labeling should describe TRITON's timing of the delivery of thienopyridines relative to the index PCI. Earlier administration of clopidogrel is probably better; this matters less for prasugrel since its active metabolite forms quicker and platelet inhibition occurs quicker.
22. Dr. Sanjay Kaul was excluded from the Advisory Committee meeting for prasugrel, on the basis that he had published numerous analyses of the TRITON data. The lateness of the subsequent process is regrettable. Dr. Kaul gave his perspective on TRITON at a meeting on 24 April 2009 with Drs. Jenkins and Temple and many of the reviewers. He presented a number of novel analyses along the lines of his published abstracts, but he raised no issues that had not been thoroughly discussed by the review team. Many of his conclusions are compatible with those expressed in this memo and in draft labeling. However, he believes the clinical importance of even minor bleeding events to be at least similar to that of many of the enzyme-only MI events in TRITON, and he finds the cancer data to be a credible risk. Although he declined to opine whether prasugrel should be approved, he feels that use beyond a few weeks should be discouraged.
23. This has not been a well managed review process. The issues were pretty clear early enough to have allowed us to meet the original PDUFA goal. What has been missing is a clear means or will to declare an end to discussions and to allow the regulatory process to complete. No one associated with this review should feel good about this.

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/s/

Norman Stockbridge
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MEDICAL OFFICER