

8. Discussion of Primary Reviewers' Comments and Conclusions

1. The primary clinical reviewer noted, "There appears to be a potential for drug-drug interaction with atorvastatin. One healthy subject in Study TAAV (Subject 115) experienced acute hepatic failure after co-administration of high-dose atorvastatin and prasugrel. Liver function abnormalities resolved after the discontinuation of both medications."

Reviewer's Comments: As noted in section 5.3, it is difficult to know the extent to which prasugrel was contributory, and the interaction occurred in only one subject. Thus, placement of a precaution in labeling seems unnecessary.

2. The primary clinical reviewer suggested that "...prasugrel should probably not be the treatment of choice in patients ≥ 75 years of age," noting that such patients appeared to receive less benefit from prasugrel, compared to clopidogrel.

Reviewer's Comments: In CURE, the study of clopidogrel versus placebo in the setting of ACS, triple endpoint event rates (cardiovascular death, MI, or stroke) for subjects ≥ 75 years of age were 17.8% and 19.2%, respectively. In TAAL, efficacy for subjects ≥ 75 years of age was similar in the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively). Thus, efficacy is marginal for both products in patients ≥ 75 years old. Importantly, however, the risk of bleeding is much higher in the elderly, and this appears to be particularly true with prasugrel. The frequencies of fatal bleeding in subjects 75 years of age and older were 1.01% for prasugrel and 0.11% for clopidogrel. The respective frequencies of ICH were 0.79% and 0.34%. With increased risks of bleeding in patients ≥ 75 in the face of marginal efficacy, the primary reviewer's recommendation seems reasonable. Some advice to the effect that prasugrel's efficacy is limited and its bleeding risk is increased in patients over the age of 75 would be appropriate for labeling.

Although the sponsor proposes a reduction in the MD from 10 mg to 5 mg daily in the over age 75 population, retention of efficacy is not assured. If prasugrel is approved for all age groups, physicians will need to carefully balance the risks versus benefits when prescribing prasugrel in patients ≥ 75 years of age.

3. With regard to the claim the sponsor is seeking for the prevention of stent thrombosis, the primary clinical reviewer originally opined that the claim should not be allowed. "Furthermore, I recommend that the sponsor participate in a randomized, prospective clinical trial to evaluate the effect of prasugrel on stent thrombosis and to determine the optimal duration of dual antiplatelet therapy. Such a trial should use the standardized ARC definitions and incorporate histopathological confirmation as well as angiographic core laboratory review."

Reviewer's Comments: Following a review of selected cases by an independent, blinded core laboratory, the primary clinical reviewer believes that the sponsor's conclusions are reasonably supported by the data. The reviewer now agrees with the claim, and no longer believes that a new clinical trial is necessary.

4. Given the concern about cancer, as well as increased bleeding risks with prasugrel over time, the clinical reviewer initially recommended "...limiting therapy with prasugrel to short-term use (i.e., one week), so that patients may receive the benefits of this therapy while avoiding some of the possible risks." The secondary reviewer recommended "...approval of prasugrel for the indication of reduction in MI in ACS managed by PCI with a boxed warning regarding cancer and a duration of treatment limited to 30 days."

Reviewer's Comments: Some members of the review team have suggested that the package insert recommend a limited duration of use for prasugrel, because of the risks of cancer and bleeding. In terms of discontinuing prasugrel, it is important to recognize that the population for whom this would be approved, i.e., patients with recent PCI, predominantly with stents, should probably not discontinue their thienopyridine, as this may lead to stent thrombosis, which is associated with poor outcomes. Thus, if the label were to encourage a limited duration of use, it would be critical for patients to switch seamlessly to another approved inhibitor of ADP-induced platelet aggregation, which presents practical problems of its own. Because continued therapy is critical, and because the risk management strategy of “switching” has not been tested, this reviewer is not enthusiastic about limiting length of use.

9. Advisory Committee Meeting

In light of what appeared to be robust efficacy findings, the Division, with concurrence of the Office, decided initially that the application should forego a public Advisory Committee meeting. Given that prasugrel appeared to be superior to established treatment for the prevention of non-fatal MI, this approach was planned in the interest of public health, so that regulatory action would not be unnecessarily delayed.

Two unanticipated issues came to light during the review process: 1) the imbalance in neoplasms between the prasugrel and clopidogrel groups; and 2) form conversion from salt to base, with bioinequivalence between the forms in the presence of a PPI. In addition, other individuals thought that a public discussion of the bleeding risk would be of value. Ultimately, the Office reached the conclusion that a public presentation of these issues to the Cardiovascular and Renal Drugs Advisory Committee would be advisable, and such is planned for February 3, 2009.

10. Conclusions and Recommendations

Although the prasugrel development program included only a single adequate and well-controlled trial to support efficacy (TAAL), the study had many of the hallmark features that provide reassurance regarding its evidence of effectiveness. TAAL was a large multicenter study with findings that were statistically persuasive, robust to exploration, and consistent across subgroups. Because TAAL demonstrated prasugrel's superiority, not to a placebo, but to an active drug (clopidogrel), prasugrel's efficacy seems beyond question. There are three key safety concerns: 1) the risk of bleeding, which is well-understood and well-characterized; 2) excess malignancies, and excess deaths in subjects with malignancies, in the prasugrel group; and 3) conversion of the prasugrel salt to free base form and bioinequivalence in the presence of PPIs. These issues generated considerable discussion between the chemistry, pre-clinical pharmacology-toxicology, clinical pharmacology, and clinical review staff within the Division, as well as staff within the Division of Drug Oncology Products, Office of Surveillance and Epidemiology, and Office of Drug Evaluation-I. Ultimately, the Office reached the conclusion that a public presentation of the complex issues to the Cardiovascular and Renal Drugs Advisory Committee would be advisable, and presentation is planned for February 3, 2009.

10.1. Bleeding

Much has already been written in the literature regarding prasugrel's risk of bleeding. Although bleeding can cause serious morbidity and mortality, the most critical consequences of bleeding, i.e., those that cause irreversible morbidity or mortality (exsanguination, MI, and stroke), were included in the primary efficacy endpoint, where prasugrel was superior to clopidogrel.

Prasugrel's benefit and risk are related to greater inhibition of platelet aggregation; although excess fatal and non-fatal bleeding in prasugrel patients is obviously unwelcome, it does not seem to outweigh prasugrel's benefit. The tradeoff between bleeding and efficacy is largely between causation of transient morbidity versus prevention of non-fatal MI. When evaluating the risk-benefit profile for a population, this seems like a reasonable trade. Given that prasugrel would be administered for secondary prevention of acute MI, the problem for the practicing physician is that s/he knows only when the drug has harmed a patient (i.e., when a patient experiences a bleeding event); but does not know when the drug has prevented an MI in a particular patient.

In summary, relative to clopidogrel, prasugrel provides a 25% relative reduction in non-fatal MI without negatively affecting survival or increasing ICH. There is much data to indicate that decreasing the frequency of MIs, even silent ones, has a favorable effect on survival, congestive heart failure, etc., although this is difficult to prove vigorously. This probable benefit, however, is weighed against a small excess of bleeding events that were emergent but did not have long-term consequences.

An additional point to consider is that the risk-benefit profile might be improved in the future, if patients at higher risk of bleeding and its consequences (patients over 75 and those with prior stroke or TIA) are excluded from treatment.

The risk-benefit profile of prasugrel can be conceptualized in starkly quantitative terms:

For each 1000 subjects treated with prasugrel instead of clopidogrel, there were:

24 endpoint events prevented:

- 21 non-fatal myocardial infarctions
- 3 cardiovascular deaths
- 0 strokes.

10 excess TIMI Major or Minor bleeding events:

- 2 fatal bleeding events
- 3 non-fatal TIMI Major bleeding events (ICH, or Hgb decrease >5 g/dL)
- 5 TIMI Minor bleeds (Hgb decrease ≥ 3 to ≤ 5 g/dL)
 - and 19 TIMI Minimal bleeds.

In terms of deaths, therefore, prasugrel treatment (compared to clopidogrel) was associated overall with 3 fewer cardiovascular deaths per 1000 subjects treated, with 2 additional deaths due to fatal hemorrhage. Overall mortality favored prasugrel by 1.4 events/1000 patients treated (p=NS).

The Division believes that this is a worthwhile risk-benefit profile for patients who might receive prasugrel. The risk should be conveyed to prospective patients through a Medication Guide, with appropriate advice on actions to take for bleeding.

10.2. Cancer

The association between prasugrel and cancer is difficult to understand mechanistically and may represent a chance finding. Nevertheless, risk of cancer is always of great interest to

practitioners and patients, and cannot be ignored. A precaution seems appropriate for labeling at this time, although others have argued for a warning or boxed warning. The risk should also be conveyed to prospective patients through a Medication Guide.

10.3. Salt to Base Conversion

The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride salt form of the drug substance had better bioavailability at higher gastric pH. Gastric acidity is germane to patients in the ACS setting, because a substantial fraction uses PPI or H₂ receptor antagonists to raise gastric pH. Thus, with the concurrence of the Division, the sponsor changed the manufacturing process to produce the hydrochloride salt form of the drug substance. Late in development, near the time that TAAL was completed, the sponsor discovered that there was significant in-process form conversion from the salt form to the base form, through an acid-base reaction.

The CMC review team and has serious concerns regarding form conversion, in that the manufacturing process fails to ensure consistent product quality, and approval of a product with significant conversion sets a poor precedent. The clinical pharmacology and biometrics review team is concerned as well, because prasugrel product with high salt to base conversion is not bioequivalent to product with low or medium conversion. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI (and, by extension, possibly a H₂ receptor antagonist). The difference in bioavailability between the high-conversion and low/medium-conversion lots is evident in C_{max}, but not AUC, and translates into reduced activity at the 0.5- and 1-hour time points. However, at 2 hours and beyond, the difference is no longer evident. This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. The delay would affect the loading dose, but would have no effect on maintenance doses.

For a number of reasons, however, the consensus within the Division is that it would be shortsighted to delay or deny approval because of the form conversion issue:

1. Prasugrel's inhibition of platelet aggregation greatly exceeds that of clopidogrel at all time points. Thus, even when conditions are most unfavorable for prasugrel (high salt-to-base conversion with high gastric pH), its pharmacodynamic effect is greater than that of the approved dose of clopidogrel.
2. The practical effect of form conversion is only a slight delay in pharmacologic action that would affect only patients on chronic PPI therapy. The delay could only be a factor for the loading dose; it could have no impact whatsoever on response to maintenance doses (consider that the peak effect of each maintenance dose, spaced 24 hours apart, is delayed by 2 hours).
3. Given that all patients receive the same dose of prasugrel, the variability in C_{max} is only moderate when compared to the variability in weight-adjusted dose between patients of higher and lower weight.
4. The variability in C_{max} due to form conversion with concomitant PPI use is small when compared to the effect of a high-fat meal.
5. The clinical benefit demonstrated in TAAL is considerable: prasugrel was found to be superior to an active comparator in preventing non-fatal MI.

6. Prasugrel's efficacy was consistent in all lots tested and across a spectrum of tablet age. Moreover, the use or non-use of PPI had no discernable effect on the efficacy of prasugrel in relation to clopidogrel.

7. In terms of safety, salt-to-base conversion is largely irrelevant. Consider that under the most unfavorable scenario, form conversion has the potential to reduce bioavailability. Thus, there is only the potential for form conversion to lead to *less* bleeding. Because Study TAAL established an acceptable safety profile for prasugrel in patients who were not using PPI or H2 receptor antagonists, and who experienced optimal bioavailability (approximately half of the overall subject population), there is little reason to worry about patients who might experience lower bioavailability.

In light of the above considerations, and in light of the public health implications of a product that has been shown to be superior to established therapy on an important outcome measure, the Division does not wish to deny or delay approval of prasugrel on the basis of this product issue.

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- The sponsor has already altered the manufacturing process to limit form conversion to some extent. The ramifications of this are two-fold:

(b) (4)

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(b) (4) If fact, the "best case" scenario for bioavailability, i.e., no effect of form conversion, has already been studied. In Study TAAL, prasugrel's bioavailability would not have been diminished in subjects who were not taking gastric pH-altering medications. (b) (4)

(b) (4)

10.4. Recommended Regulatory Action

The Division recommends approval of prasugrel for reduction of myocardial infarction in patients with ACS who are managed with PCI. The claim sought by the sponsor, the reduction of "atherothrombotic events," is ambiguous and implies reductions in all 3 components of the TAAL

primary endpoint. The indication should be restricted to reduction of myocardial infarction, the component where efficacy was actually demonstrated.

It could be argued that the results of TAAL show prasugrel to be non-inferior to clopidogrel in ACS, such that it is appropriate for prasugrel to enjoy the same claims as its comparator. Clopidogrel has the indication “for the reduction of atherothrombotic events as follows: ACS:...to decrease the rate of the combined endpoint of cardiovascular death, MI, or stroke....”.

Although clopidogrel has a claim for “reduction of atherothrombotic events,” the phrase seems inappropriate in retrospect. For cardiovascular death and stroke, the rates with clopidogrel were only marginally better than placebo, and the differences were not statistically significant. The ambiguity in the phrase “atherothrombotic events” mostly serves to encourage loose association and extrapolation.

Some of the reviewers in the Division and some staff in OSE would limit the length of prasugrel’s use to manage the risk of bleeding or to address concerns regarding possible cancer. As noted in this review, there is no clear rationale for selecting a specific length of time. Moreover, mandating or encouraging a limited duration of therapy requires switching to another drug, and this type of risk management strategy has not been tested in the post-PCI setting. By avoiding use of prasugrel in patients at higher risk of bleeding (patients over the age of 75, patients with prior stroke or TIA, and patients who are planned to undergo CABG or other surgery), much of the excess bleeding risk will have been avoided. In terms of cancer risk, lacking definitive data, the strategy of limiting length of use seems ill advised.

10.5. Risk Evaluation and Mitigation Strategy (REMS)

FDA can require a Risk Evaluation and Mitigation Strategy (REMS) for a known or potential serious risk if we find it necessary to ensure that the benefits outweigh the risks of the drug. After extensive internal discussions and consultation with the Office of Surveillance and Epidemiology (OSE), we propose REMS that include:

- A Medication Guide rather than a PPI as stated above
- A Communication Plan to healthcare providers that includes information including:
 - appropriate patient selection, emphasizing that prasugrel should not be used in patients older than 75, or patients with prior history of TIA or stroke
 - the risk of bleeding and instructions on management
 - information on the potential risk of malignancies and need for monitoring

There is ongoing discussion regarding the need to initiate prasugrel in the inpatient setting.

10.6. Postmarketing Requirements

The cancer concern should be addressed through a randomized, controlled clinical trial. Whether or not the ongoing outcome trial would be sufficient to address the issue is under continuing discussion. A registry may be supportive, but could not substitute for a randomized controlled trial. The details of the study(ies) will need to be worked out and agreed upon prior to approval.

10.7. Other Postmarketing Commitments

- The sponsor has initiated Study TABY, a ~13,000 subject study comparing prasugrel to clopidogrel in the UA/NSTEMI patient population, managed without PCI. The study is

evaluating a lower loading dose of 30 mg, and a lower maintenance dose (5 mg) in subjects over age 75 or weighing <60 kg.

- The sponsor has established a registry to follow stent thrombosis.

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/s/

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