Reviewer's report

Title: Long-term safety, tolerability and pharmacokinetics of the highest available dose of paliperidone palmitate: a one-year open-label study in patients with schizophrenia

Version: 1 Date: 14 July 2011

Reviewer: Alberto Parabiaghi

Reviewer's report:

• Major Compulsory Revisions

In the Title, and throughout the text, the expressions “long-term” and “open-label” should be avoided. A 12-month trial should not be considered long-term, since, for schizophrenia, average duration of illness and treatment is quite longer, and since steady state for long-acting injectable formulations is usually reached after months (8/9 months for PP). The use of the term “open-label” is misleading, as it is usually used for randomized comparisons. The expression “observational” is preferable. I suggest to define the study as a phase-1 observational study since the study aim is to examine the long-term pharmacokinetics and tolerability of the highest available dose of PP, the patients who dropped out from this dosing regimen should be considered separately. Classifying patients in Treatment A and B is confusing. Actually, patients on Treatment B dropped out from Treatment A.

Out of 212 patients, 104 (49%) completed the study receiving the 150 mg eq. dose regimen for the entire period. I believe that those subjects should form the primary analysis group and could be called “continuers” or “completers”.

Dropouts should be considered altogether (Treatment A discontinuers: n=86 + Treatment B discontinuers: n=13 + Treatment B flexible dose: n=9 --> n=102) and could be called “discontinuers” or “non-completers”.

Comparisons in terms of baseline characteristics and follow-up endpoints of efficacy and tolerability between continuers and discontinuers should be performed.

The group of subjects to be included in the assessment of safety and tolerability is often called “safety analysis set” and is often defined as those subjects who received at least one dose of the study medication. I appreciate this approach. However, the safety analyses should include a comparison between continuers and discontinuers as well.

At page 12, “Pharmacokinetic analysis” please specify the number of subjects included in the “Pharmacokinetic analysis set” (n=100?)

I suggest to cut off the paragraphs on the Population-PK model evaluation both
in the Methods and in the Results section (and Figure 2). This analysis could be the subject of a following brief report or letter.

In the Discussion, authors should interpret their findings in light of the results of the comparisons between continuers and discontinuers, keeping in mind that the study is meant to answer one principal question: Do these preliminary results support recommendation of the proposed dosing regimen? If yes, authors should propose further exploration the advantages of the proposed dosing regimen through randomized comparisons --> Which could be the advantages of this dosing regimen in comparison to a more flexible one?

In this observational study, treatment with highest available dose of PP resulted safe and tolerable in the medium term (one year) in half of the sample. What the authors wrote at page 20 (lines 10-13 of the Discussion) is questionable. Results do not attest directly to the tolerability of the proposed dosing regimen in long-term therapy.

The authors should thoroughly discuss the reasons for discontinuing the proposed dosing regimen. It resulted in fact practicable for only half of the included subjects and, generally speaking, a 50% discontinuation rate is not low for a long-acting formulation in stable, young schizophrenic subjects without hypersensitivity to paliperidone or risperidone (or their excipients).

Page 22, line 4: it is questionable to argue that, since underlying factors for glucose-related adverse events were identified, PP could not be the primary cause. Those subject had rather been excluded from the beginning.

At page 23, the authors wrote: “The lack of a placebo group...”. This make little sense, since no comparison was planned. The lack of an experimental (or even a quasi-experimental) design requires caution in interpreting these findings. The main problem is that a comparison (blinded or unblinded, randomized or not) was not prospectively planned and the post-hoc comparisons I suggested above cannot solve the problem.

• Minor Essential Revisions

Methods, second line: #70

Figures 1-5 (page 38 onward) should be renumbered and captions should be included.

• Discretionary Revisions

None

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

The Mario Negri Institute for Pharmacological Research, with whom I am affiliated, has received unrestricted funding from Bristol-Myers Squibb to run the GiSAS trial, a pragmatic RCT on aripiprazole, olanzapine and haloperidol in the long-term treatment of schizophrenia. I declare that I have no competing interests and that I have no past, current or pending financial link to any pharmaceutical company other than the research support administered for the GiSAS trial conduct.