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: 10 August 2011

Reviewer: David Kemp

Reviewer’s report:

MAJOR REVISIONS

1. My greatest concern with the paper is that it does not go far enough to impart clinical recommendations given the extensive amount of collected data. The audience for this journal likely includes many practicing psychiatrists and even consumers who have open access. Thus, it may be advantageous to distill the findings into clinically pragmatic messages that can be utilized in day-to-day patient care. Some specific areas than can be addressed include the following:

A) Do data show any inconsistency in bioequivalence when administered in gluteal muscle as compared to deltoid muscle?

B) Is any overlap in oral paliperidone necessary prior to solely using paliperidone palmitate? How do the data answer this question?

C) There is an opportunity to look at how the results were impacted by ethnicity, given the diversity of the current study with enrollment of a large number of Asian and African-American participants. What do the data tell us about ethnicity?

D) It appears that 97% of steady state is achieved after 41 weeks of administration. How does this value relate to the pharmacokinetics after the first or 2nd injection? What are the clinical implications around this finding?

2. The results indicate that schizophrenia (5%) and psychotic disorder (3%) were serious treatment emergent adverse events. I’m confused as to how schizophrenia is an adverse event. My understanding is that all patients were diagnosed with schizophrenia in order to enroll in the study. Perhaps it is being implied that patients are experiencing a worsening of psychotic symptoms? In this case, are the early discontinuations due to poor symptom control?

3. Please indicate how many patients had worsening in PANSS score of 20% or greater and 30% or greater.

4. Were any differences observed in the side effects among the higher dose and flexible (lower) dose groups (i.e. dose related side effects)?

5. It is reported that 78% of patients had treatment-emergent abnormal prolactin levels, particularly among women. Can the authors expand upon this finding
within the discussion as to the clinical implications:

A) What recommendations are being made regarding the prolactin findings? Should patients be continued on treatment despite elevated levels if asymptomatic? Should monitoring of prolactin levels occur at specific intervals?

B) How does the rate of elevated prolactin compare with oral paliperidone?

C) Some discussion about the potential long-term risks appears indicated. For instance, how might this affect menstruation, libido, and osteoporosis?

D) Were patients specifically queried for side effects related to hyperprolactinemia? For example, some of the side effects that might include difficulty with sexual functioning or galactorrhea may be embarrassing for patients with schizophrenia to spontaneously report and may be underestimated if they were not raised on direct questioning.

MINOR REVISIONS

1. The eligibility criteria in the abstract (Methods) states the PANSS total score is =70. Is this a typo, as in other places it states <= 70?

2. On page 19, the prolactin concentrations among women are reported to decrease to the Day 372 timepoint. In Figure 5, although there is a gradual decrease to Day 372, at endpoint there appears to be a rise in the slope again. Please discuss what accounts for this change and how the endpoint differs from the Day 372 timepoint (are these LOCF findings?).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am on the speakers bureau for AstraZeneca and Pfizer. I am a consultant to Bristol-Myers Squibb. I am currently considering participation in a Work Group on long-acting injectable therapies that is sponsored by Janssen.