Reviewer’s report

Title: Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis

Version: 1 Date: 28 July 2008

Reviewer: John H Kalbfleisch

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MAJOR COMPULSORY REVISIONS

The manuscript seems to require a meta-analysis approach – clarity in the statistical methodology is needed. Elaborate data procurement and analysis in methods.

1) Provide a description of the analysis procedure used to obtain results in the tables. Explain how the “between study” variable (there were 12 studies used) was accounted for in the analysis procedure. If frequency counts of the 12 studies were simply combined (as if in a single large study) then this should be stated. See comment 3).

2) “Methods” should identify the inclusion and exclusion criteria used for selecting studies that were used to achieve composite results.

MINOR ESSENTIAL REVISIONS

3) Did the 12 studies give the same (similar) group comparison results, or were there conflicting indications between studies for (important) outcomes? How many of the 12 studies showed the reported conclusion in the manuscript (or how many gave a different conclusion).

4) In addition to the 95% CI’s the authors could consider showing levels of significance associated with comparing group rates. Because of the number of comparisons presented in the tables via 95% confidence intervals, some Type-I errors are expected.

5) Major sections of the manuscript have mixed content and a revision is suggested.

(statements of methodology belong in Methods, results in Results and so on)
6) Mention unreported outcomes with a rate < 1% (as text - unless there are too many). There are some tables that report rates less than 1% - an apparent conflict with statements “that only rates 1% and higher are shown.”

7) Follow the usual table publication format. Omit most horizontal and vertical lines between adjacent rows/columns and remove the horizontal black bar in Table 7.

8) Authors could consider 2 decimal places (instead of 1) for reporting 95% CI limits. This is an attempt to be clearer for “0” endpoints of the CIs. Which strategy was used for rounding to report % values (round-down, round-up or round-off)?

DISCRETIONARY REVISIONS

9) Incidence is the numerator (count) for an incidence rate. Since he treatment effect is evaluated by comparing group rates, I would suggest using “incidence rate” instead of “incidence” throughout the manuscript.

10) Summary statistics in the tables are N (%). The % is a rate and most of these seem to be incidence rates. Some rates (table 4) might be viewed of as prevalence rates (outcomes that occur before study enrollment and then recur during the study are not “new” recurrences), however, groups are still compared on the reported rate statistics.

11) Authors state that rates of drug-related adverse experiences and discontinuations due to drug-related adverse experiences were higher in the non-exposed group, “primarily due to the increased incidence of hypoglycemia in this (non-exposed) group.” However, there is no supporting evidence for this explanatory statement. It seems that the data analysis could show if drug-related adverse events are more frequent in participants reporting hypoglycemic experiences (thus providing supporting evidence).

12) In the “Competing Interests” section, consider a brief statement that addresses the “conflict of interest” outside of employment. I find myself asking if there are studies that were excluded (see inclusion and exclusion in Major Compulsory Revision) because of the result they produced. If all available studies were used, then a statement to that effect should be made. All 12 studies were published, were unpublished studies excluded?

13)
“Pooling” is mainly a statistical term. An alternative descriptor (combining, composite) might be understandable/informative to more readers. The authors are not clear on the statistical methodology for pooling.

14) This is a question or comment I have. Were the groups similar if the study-time is considered for rates? Were some outcomes observed immediately or early in studies and in similar fashion for both study groups? (similar for outcomes occurring across a 2 year) Groups rates could be similar but one group could experience the adverse outcome sooner than the other group (a survival type analysis could detect this).

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare I have no competing interests.