Author’s response to reviews

Title: The Sertindole Safety Survey: a retrospective analysis under a named patient-use program in Europe

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Version: 3 Date: 21 April 2008

Author’s response to reviews:

Dear Editor John Kerr

Revision of article: The Sertindole Safety Survey: a retrospective analysis under a named patient use programme in Europe.

Please find attached our revised manuscript, and our responses to your reviewers’ questions. We have taken into account all the points raised by the reviewers, and either incorporated the additional required information into the manuscript, or provided the reviewer with an explanation of our reasons for not doing so. Changes are all shown in track changes mode to enable ease of comparison.

Please note that we have corrected an error in the document. Portugal should have been mentioned in the group of countries that ceased to allow prescription of sertindole after the market suspension, and we have thus altered the text accordingly.

Regarding Reviewer 2’s point number 12, we appreciate fact that the statistical tests suggested could be done, but we feel that this would not be the most appropriate way to reflect the study results. However, if the editorial board would like us to do these tests, we will of course happily oblige.

We greatly appreciate the input of the two reviewers; their objective comments have enabled us to see where the manuscript was lacking in clarity, and we hope that it will now meet with their approval for publishing. Should there be any future unclear issues, we will of course do our utmost to clarify these further.

We thank you for the revision extension time that you granted to us. We look forward to hearing from you in due course.

Yours sincerely,
On behalf of also Dr. Ch. Lançon, Dr. Mondher Toumi, and Ch. Sapin
Karina Hansen

Response to Reviewers

Reviewer 1: Tilman Steinert

1. The reviewer’s understanding of the inclusion criteria is correct, and we have added text to the inclusion criteria section to clarify the situation for future readers.

2. We have edited the text in this area, and believe that taking into account the additions made to the inclusion criteria section (see response number 1), this is now clearer. In order to make Table 3 more self-explanatory, we have added the definitions of the “Before” and “After” subgroups to it.

3. We thank the reviewer for pointing out this error in the text. The text should, of course, read ‘At the time of their last physician visit, more than half of the patients were still being treated with sertindole.’ We confirm that the inclusion criteria given in the original text, and the additional information we have added during this review, are correct. Table 4 has been revised to be more easily read.

4. In fact, what is being referred to here is the proportion of patients who, having received sertindole during the market suspension (whether in the “Before” group or the “After” group), had to stop the treatment due to the problems of drug supply and associated administrative difficulties that surrounded the NPU programme. As can be seen from Table 4, this proportion was around 30% (35.3% in the “Before” group, and 26.8% in the “After” group). This is not in contradiction with the inclusion criteria, and we hope that following the changes we have made to the manuscript (see response 1 above) concerning the inclusion criteria, the reasoning for our statement is now clearer.

5. The four ‘other deaths’ were due to the following causes: pulmonary embolism in a patient suffering from Steele-Richardson-Olszewski disease; unspecified intoxication; myocardial infarction; and mesenteric artery infarction. We have added this, and other information, into the safety chapter.

6. In order to clarify the causes of the other SAEs, we have expanded Table 6 to include details of the SAEs occurring more than once. Overall, the majority of SAEs were psychiatric (24, of which 20 were psychosis). These were considered to be part of the natural course of the disease and therefore classified as relapses; they accounted for 27.59% of SAEs, and explain the high level of SAEs under the heading of ‘other’. The remaining SAEs were one event each of the following: abnormal ECG; accident; angina pectoris; deep thrombophlebitis; galactorhea; hallux valgus; impotence; myocardial infarction; oedema; pregnancy; rash; self mutilation; vomiting; and weight gain.

We note that questions 7 to 9 have been omitted.

10. We agree that this table is superfluous, and have added the information into the text.

Minor essential revisions – reviewer 1
1. The number of included patients and information on rates of QTc prolongation have been added to the abstract.

2. Under the Named Patient Use programme, physicians wishing to prescribe sertindole were required to request permission from the relevant health authority. Each individual countr involved set up its own NPU programme. Patients on the NPU programme were those that were previously well controlled on sertindole, and those that, after 2000, were prescribed sertindole as a last resort treatment.

3. The numbering of the tables has been rectified.

4. We accept the criticism that there is some repetition of results in the discussion section, but the Sertindole Safety Survey was carried out in very unusual circumstances. There was an enormous bias present and irrevocably inbuilt in the study, which we considered in the discussion section. As there are no other directly comparable studies, our comparisons with available literature were limited, but we did consider relapse rates, use of concomitant antipsychotics, and other post-marketing studies. We also considered the duration of exposure, and the possible effects of adverse publicity. In addition, we considered other study limitations. We believe that we have drawn as much information as possible from the study, and discussed it as far as possible. The intention behind the study was to provide further information for the regulatory bodies, and we believe that it is important to transmit this information to practising physicians.

Regarding Torsades de Pointes, we agree that it is unlikely that this would be found in a routine ECG. However, in the patients being admitted to hospital due to an SAE, ECGs taken on admission could not be considered as routine. None of these ECGs showed Torsades de Pointes. It is difficult to say how probable it would be that Torsades de Pointes accounted for the cases of sudden death, as a multitude of factors could be involved in the development of this arrhythmia (such as long QT syndrome, hypokalaemia, bradycardia, drug induced QT prolongation and diabetes). Titier et al explore this issue in their review article entitled “Atypical Antipsychotics, from potassium channel to Torsade de Pointes and sudden death” (Drug Safety 2005:28 (1): 35-51). These authors point out that it cannot be assumed that if the prolongation of the QTc interval is increased, the risk of dysrhythmia or sudden death is increased in all patients.

We apologise, but we do not quite understand the point about the first sentence of the discussion being in contrast with the inclusion criteria.

Reviewer 2 Jari Haukka
1. We thank the reviewer for these additional references; we have incorporated them into the article.

2. We have added information as to how data were gathered into the methods section. The gathering could not follow uniform procedures due to the differing national situations.

3. The case report form (CRF) was designed to collect data in a retrospective way. The details of all the information that was collected and analysed are given in the ‘Data collection’ part of the manuscript. Information about the causal relationship between sertindole and SAEs, in the opinion of the reporting physician, was also requested. However, this information was not analysed, and is therefore not mentioned in this manuscript. We think that it would be unusual to include the CRF as an attachment, and in fact this would give the reader very little additional information. We have included instead the possibility for any interested reader to obtain a copy on request, and should the reviewer require a copy, we will be happy to supply him with one.

4. We have expanded the explanation of exposure. During the study period, none of the patients restarted sertindole after they had discontinued.

5. Discontinuation was considered to occur when a patient ceased to be prescribed sertindole. The CRF asked for the starting date of sertindole treatment, and the end date of treatment for those patients that stopped sertindole before the study end. No details were asked for regarding patient compliance, and exposure was calculated on the assumption that patients took the tablets prescribed. We acknowledge that this is a weakness in the study design, but as this is a retrospective study, it would be unlikely that patients or physicians would have been able to recall the finer details of compliance.

6. From a purely statistical point of view, some patients could be considered as censored, since they were still treated with sertindole at the end of the study period. However, since the aim of the study was to assess the patterns of prescription of sertindole in the specific context of an NPU programme, survival analyses were not retained in the statistical plan.

7. We have added in more detailed information regarding the causes of death.

8. ICD-10 coding was not used in this study. The diagnoses recorded in the database were made by the individual reporters, and they were not changed unless the reporter agreed to the proposed change.

9. We agree with the reviewer that the analyses of discontinuation would have been interesting to address, using survival models accounting for background variables. However, there is a major selection bias irrevocably inbuilt in the study due to the fact that the NPU programme was imposed by the Health Authorities. The population included in this study is therefore not representative of the patients suffering from schizophrenia, and even not representative of patients eligible to sertindole treatment, due to this selection bias. As a result, any modelling approach aimed at defining the determinants of a phenomenon linked to sertindole (for instance, discontinuation) or the disease evolution (for instance,
relapse) would have led to biased results; these reasons led us not to perform such analyses in this context.

10. Please see previous answer.

11. Age quartiles have been added into Table 1.

12. As the aim of the manuscript was to describe the prescription patterns of sertindole via an NPU programme, we planned not to perform any statistical tests. Furthermore, the test of independence would not be valid due to the nature of the variables that are cross-tabulated: for Table 2 (number of antipsychotics prescribed prior to sertindole initiation crossed by the type of antipsychotics), some cells are necessarily empty and automatically impact the result of the test.

13. With all due respect to the reviewer, owing to the constraints of the NPU programme and the high level of supervision surrounding the patients on it, we consider that if a patient received the treatment, his/her attending physician must have considered extremely carefully the possible benefits and risks associated with giving sertindole to that particular patient. Thus, we believe that the medication was thought to be necessary for these patients’ individual wellbeing, and in consequence sertindole was not simply used because it was available, but because it was truly needed. We therefore think that our statement is justified, and we believe that it should be retained.

14. We have corrected the table numbering.