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APPLICATION NUMBER:

022036Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: December 2, 2009

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-036

SUBJECT: Action Memo for NDA 22-036, for the use of Silenor (doxepin HCl) in the treatment of insomnia

NDA 22-036, for the use of Silenor (doxepin HCl) in the treatment of insomnia, was submitted by Somaxon Pharmaceuticals on January 7, 2008. The application was submitted as a 505(b)(2) application, relying on the approved applications for Sinequan (doxepin) capsules and Oral Concentrate, as well as Zonalon (doxepin) Cream. Sinequan is approved and has been marketed since 1969 as an anti-depressant and anxiolytic at doses up to 300 mg/day (usual daily dose of 75-150 mg/day). Zonalon Cream is a topical preparation and is indicated in the treatment of pruritis.

The initial application contained the results of 6 controlled trials. The Agency issued a Complete Response (CR) letter on 2/25/09; the primary reasons for this action were as follows:

Effectiveness

The division primarily considered the evidence purporting to establish substantial evidence of effectiveness for Silenor as a treatment for insomnia characterized by difficulty in maintaining sleep (there were no consistent positive findings on measures of sleep latency). However, we had concluded that there was inadequate subjective evidence of sleep maintenance (as assessed by the subjective [sWASO]) in non-elderly adults at the 6 mg dose. Specifically, although there was objective evidence of an effect (as measured by objective Wake Time After Sleep Onset [oWASO]) on sleep maintenance at days 15 and 29 in non-elderly adults, there was no evidence of a beneficial effect on those nights on a subjective measure of sleep maintenance (sWASO) in this population, the protocol-specified primary nights at which a subjective response was to be measured. There were statistically significant drug-placebo differences on nights 16 and 30 on sWASO in this population at this dose, and on the mean of Nights 15 and 16 and 29 and 30. There were also significant findings on sWASO out to 2 months in elderly adults (in a separate study) at 6 mg, but, as noted in the CR letter, we could not be certain that the effects seen on subjective measures at 6 mg in the elderly were applicable to non-elderly adults (possibly because of the higher plasma levels achieved in the elderly

compared to the non-elderly at this dose, or perhaps related to increased sensitivity to drug effect in the elderly).

Further, we noted that there were significant subjective findings on oWASO in the non-elderly population at 3 mg out to one month, but no significant findings on sWASO in this population after Night 1 (and no robust effect on sWASO in the elderly at this dose). Taken together, the division concluded that there was no clear effect on subjective measures of sleep maintenance at any dose in the non-elderly population.

Safety

The division concluded that there was evidence that Silenor might have been associated with a prolongation of the QT interval of between 5-10 msec. We were aware at the time we issued the CR letter that the sponsor had performed, or was in the process of performing, a thorough QT study, and in the letter we asked the sponsor to submit the results of this study.

The sponsor responded to the CR letter with a complete response on 6/4/09. The response primarily consisted of additional statistical analyses performed in an effort to provide evidence that there were robust effects on subjective measures of sleep maintenance at a 6 mg dose in the non-elderly population. This submission has been reviewed by Dr. June Cai, medical officer, Dr. Abiola Olagundoye, SEALD, the Interdisciplinary Review Team for QT Studies, Dr. Tristan Massie, statistician, Jessica Diaz and Melissa Hulett, Division of Risk Management, and Dr. Ronald Farkas, neurology team leader. In this memo, I will very briefly review the relevant issues, and offer the rationale for the division's action.

As noted above, the sponsor has submitted the results of additional statistical analyses that they believe establish a reliable effect of Silenor 6 mg on sWASO.

Specifically, as discussed by Dr. Massie, the sponsor asserts that the treatment by time interaction is not statistically significant for the 6 mg dose based on a Mixed Model Repeated Measures (MMRM) analysis, on the basis of which they conclude that the average treatment difference over the double-blind period can stand for the difference at the end of the study. On the basis of this new analysis, the sponsor obtains a significant drug-placebo difference. Based on the MMRM, differences between 6 mg and placebo at days 15 and 16 did not reach statistical significance nor did the 6 mg-placebo difference reach significance at Night 29 (see Dr. Massie's Table 6), though the between-treatment contrasts for the average of each two night pair does reach nominal significance (see Dr. Massie's Table 8).

However, according to Dr. Massie, the power of this test to detect an interaction is quite low (43%). For this reason, we cannot with confidence reject the hypothesis that there is no treatment by time interaction.

For example, Dr. Massie notes that the p-value for the interaction test based on the first night of each visit is 0.14. Including all nights for each visit, the p-value for the test of the interaction between time and treatment is 0.27. However, for a test of 90% at the 0.05 significance level, the null hypothesis of no interaction would be rejected if the p-value for the interaction test was <0.54. For a test with 80%, we would reject the hypothesis of no interaction with p<0.33.

In addition, a simple inspection of the data suggests that the treatment effect is not constant over time. In this regard, see Dr. Massie's Figure 1, which depicts the mean sWASO over time (at Nights 1 and 2, 15 and 16, and 29 and 30), and clearly documents the inconstant pattern of responses, especially at the end of the study. In fact, the difference in treatment effect between Nights 29 and 30 is statistically significant. This makes it difficult to reliably estimate the true treatment effect at the end of the study, making comparisons between this (unknown) treatment effect and estimates of the treatment effects at earlier timepoints unreliable.

Further, as Dr. Massie notes, there were likely not sufficient assessments during the 30 days of the study to conclude that the treatment difference was constant at times between assessments.

For these reasons, then, in his view, for an assessment of the drug effect at the end of the study, we must continue to rely on the data at that time point (that is, at Nights 29 and 30; again, the assessment at Night 29 was specified in the protocol as the primary assessment).

In addition, the sponsor also applied an MMRM approach to subjective Total Sleep Time (sTST), their preferred subjective measure of sleep maintenance. Using this analysis, statistical significance was not achieved for either Night 29 or Night 30.

The sponsor asserts that a pre-specified plan for performing the MMRM analysis was followed, though they acknowledge that this plan was proposed after the submission of the NDA (that is, after the data and results of the previous analyses were obviously known).

Finally, Dr. Massie performed calculations to determine the potential size of the interaction that could not be excluded, with an eye to examining whether or not the difference in the size of any treatment effect among timepoints might be sufficiently small to be considered unimportant. As he notes, the findings on the MMRM performed by the sponsor are consistent with a treatment difference on Nights 15 or 29 of about 10 minutes less than on Night 1. This difference is

about 50% of the estimate of the treatment difference at Night 1, a difference that seems non-dismissible.

Safety

The sponsor has submitted the results of a thorough QT study examining doxepin doses of 6 and 50 mg. The QT Review Team has concluded that neither dose is associated with a meaningful increase in the QT interval.

Conclusions

The sponsor has submitted numerous additional analyses that purport to establish a consistent effect of a 6 mg dose of doxepin on subjective measures of sleep maintenance in the non-elderly population out to one month. The statistically significant between-treatment differences that the sponsor presents, however, are as the result of MMRM analyses performed after the original data were known and analyzed. Further, and importantly, the results are based on the presumption that there is a constant treatment effect over time, and that there is no treatment by time interaction. Although the sponsor's formal test for such an interaction did not reach significance, Dr. Massie points out that the power to detect such a difference was very small (43%). Inspection of the data also suggests that the effect may not have been constant over time (and that there were likely not sufficient assessments over the 30 days of the study to permit a conclusion that the effects were constant over time). For these reasons, we cannot accept the sponsor's assertions that the MMRM analyses are appropriate. As a result, I believe that we should rely on the original analyses on which we based our original decision.

I note that Dr. Farkas continued to recommend that the application be approved. He bases this conclusion on his original reasoning, and he acknowledges that the sponsor has presented no new statistical arguments that persuasively counter the reasons for the initial CR action. In short, in his view, no meaningful change in the data package has occurred, and so his original conclusion still applies. I agree that the sponsor has provided no new arguments that adequately address our concerns, as articulated in the original CR letter, and which transmitted my decision to not approve the drug at that time. Although I note Dr. Farkas's recommendation, I have not changed my original views, and, for this reason, will issue the attached CR letter.

Russell Katz, M.D.

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