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APPLICATION NUMBER:

022036Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: March 16, 2010

FROM: 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) as a treatment for insomnia characterized by difficulty with sleep maintenance

NDA 22-036, for the use of Silenor (doxepin) as a treatment for insomnia characterized by difficulty with sleep maintenance, was submitted by Somaxon Pharmaceuticals, Inc., on 1/31/08. The division issued a Complete Response (CR) letter on 2/25/09, noting that substantial evidence of effectiveness had not been submitted.

Specifically, the approval of hypnotic products has traditionally been supported by both objective (polysomnographic; PSG) and subjective (patient report) evidence of effectiveness. In this NDA, the division had concluded that adequate subjective evidence of effectiveness in non-elderly adults had not been demonstrated. In particular, the sponsor had submitted the results of a study (Study 501) in which subjective effects of Silenor on sleep maintenance were assessed at Days 1 and 2, 15 and 16, and 29 and 30. Although statistically significant effects were seen on the average of nights 15 and 16, and on the average of nights 29 and 30 (as well as on nights 16 and 30), there were no statistically significant findings on nights 15 and 29, the nights specified as primary in the protocol. Statistically significant findings on subjective measures were seen in a study in elderly patients out to 2 months. In addition, in the 2/25/09 CR letter, concerns about QT prolongation were raised.

The sponsor responded to the CR letter in a submission dated 6/4/09.

In this response to the CR letter, the sponsor primarily provided the results of a Mixed Model Repeated Measures (MMRM) analysis of Study 501, which demonstrated statistically significant changes on the subjective measures for the entire study. The possibility that such an analysis might be considered useful had been discussed with the sponsor at a meeting after issuance of the first CR letter. In addition, our previously expressed concerns about QT prolongation were adequately addressed.

Subsequent to this submission, the division issued a second CR letter on 12/04/09. In that letter, numerous deficiencies in the MMRM analysis were described.

In response to the second CR letter, the sponsor submitted a request for a Type A meeting to discuss the NDA. A meeting was held on 1/20/10.

In the briefing book submitted in advance of the meeting, the sponsor made several additional arguments in support of approval of the NDA. This briefing book was subsequently submitted on 1/21/10 as a Complete Response to our 12/4/09 CR letter.

First, they argued that the lack of consistent subjective findings after Day 1 should pose no bar to approval, (b) (4) Further, they proposed that, if the Agency determined that the lack of a consistent finding on subjective measures in the non-elderly made it impossible to conclude that substantial evidence of effectiveness had been provided for this population, the Agency could approve Silenor only for use in the elderly. In the sponsor's view, such an approach would be consistent with the law. The sponsor further supplied additional arguments to support the appropriateness, and results, of the previously submitted MMRM analysis, and provided results of additional analyses that they suggested support a finding of consistent significance for the subjective measures for the entire duration of Study 501. The sponsor also made the point that studies of previously approved hypnotic drug products did not always provide consistent findings on both objective and subjective measures for the duration of all studies. These issues were all discussed at the meeting with the sponsor on 1/20/10.

I have re-examined the evidence submitted and the sponsor's most recent submission and arguments.

Although I do not find several of these arguments to be particularly compelling, I now conclude that the application may be approved.

In particular, I do not believe that substantial evidence of effectiveness can be considered to have been submitted if there was no evidence of subjective improvement beyond Day 1. That is, I cannot accept the sponsor's argument that such an outcome would be acceptable because it can be (b) (4) I believe that, until and unless our standards change in this regard, we should have evidence of subjective improvement beyond the first few days for an effective hypnotic. Similarly, I do not find the sponsor's argument that the absence of substantial evidence of effectiveness in the non-elderly population does not preclude approval in the elderly. Although I agree that one could fashion an argument that such an approval is supported by law (b) (4)), such an outcome would be unprecedented (at least for hypnotics) and would set an unfortunate precedent.

However, I have re-considered the sponsor's arguments justifying the use of the MMRM, as well as their arguments pertaining to precedents for hypnotic drug approvals.

The sponsor argues with our claims, expressed in the CR letter of 12/4/09, that the MMRM analysis could not exclude a treatment by time interaction. I take the sponsor's point that the test that they used, and the standard they applied, to exclude such an interaction were entirely standard, and that our objections in this regard were based on a standard not previously employed. We had also raised objections to the analysis based on the fact that it was chosen after the sponsor knew the results of the study. Although this is, of course, true, as the sponsor points out in their briefing book, this was also, of course, well known to us when it was discussed as a possibility at our meeting on 1/20/10. The sponsor also notes that the plan was pre-specified, in the sense that it was planned without regard for the specific data, and itself was entirely routine in structure.

I further note the sponsor's depiction of various precedents, in which other hypnotic drugs were approved in the face of somewhat contradictory findings on subjective and objective outcomes, as well as in the face of effects that clearly diminished over time, in some cases over durations much shorter than 1 month.

I have also re-evaluated the fact that the findings on the subjective measures were clearly significant when the 2 days at each time point were averaged. Although this was not proposed as primary in the protocol, I now believe that this maneuver is not inappropriate, and has been performed for other drugs in the past. And seen in a different light, the clear significance out to 3 months on objective measures in the elderly at 3 mg (one-half the dose proposed for the non-elderly), as well as the clear significance on both objective and subjective measures at 6 mg in the elderly out to 2 months, and the clear significance on objective measures at one month in the non-elderly at both 3 and 6 mg all support the finding that Silenor provides a clear hypnotic effect. Although the lack of a completely consistent effect on subjective measures is of some concern, on further reflection I do not believe that it precludes approval.

For the reasons given above, then, I will issue the attached Approval letter, with attached labeling to which the sponsor and we have agreed.

Russell Katz, M.D.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22036	ORIG-1	SOMAXON PHARMACEUTICALS INC	SILENOR (DOXEPIN HCL)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
03/17/2010