

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-272/S-036/041

NDA 20-588/S-024/028/029

NDA 21-444/S-008/015

OFFICE DIRECTOR MEMO

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 14, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for Risperdal (risperidone) for the treatment of irritability associated with autistic disorder

TO: File NDAs 20-272/S-036, 20-588/S-024 and 21-444/S-008
[Note: This overview should be filed with the sponsor's 1-16-06 response to FDA's 5-19-05 not approvable letter.]

The original supplement was submitted 12-19-03 and an approvable letter was issued 6-18-04. A major concern noted in this letter was the failure to establish the optimal dosing strategy for treating this new indication. The concern was that patients might be receiving higher doses than needed. This concern was based in part on a finding of a somewhat higher incidence of various adverse events in the autism studies than was seen in other studies with this drug. The letter noted that there would be a need for a dose response study to better establish the dose response relationship for this drug, but did, nevertheless, offer the sponsor the opportunity to try to establish reasonable dosing recommendations for labeling based on existing data. The letter also included a request for juvenile animal toxicity studies in 2 species, and for various other information.

The sponsor responded to the 6-18-04 approvable letter on 11-18-04. This response included a (b) (4) acknowledging that the flexible dose design of these trials precluded reaching any definitive conclusions about the dose response relationship. The division (DNDD) considered and rejected these arguments and maintained its position that the sponsor had not identified a lowest effective dose and had not justified the use of the higher doses recommended in labeling. The basic concern again was unacceptable adverse effects. Thus, a not-approvable letter was issued 5-19-05.

The sponsor requested a meeting to discuss the 5-19-05 NA letter, and the psychiatry division (DPP) met with the sponsor on 12-7-05. In a background package for this meeting, the sponsor made several arguments:

-Regarding the concern about unacceptable adverse events, the sponsor noted that adverse events were largely mild to moderate in severity, similar qualitatively to those seen in adults, transient, and led to discontinuation very infrequently (1.3%). They further argued that the somewhat higher

incidence of adverse events was partly an artifact of using a questionnaire to elicit adverse events and partly due to the fact that many of these patients were naïve to risperidone, unlike patients in other programs.

-They argued that a recoding of certain adverse events as suggested by FDA led to even less of a signal for unacceptable adverse events for risperidone.

-They also argued that the expressed concern about unacceptable longer-term risks, in particular, TD, hyperprolactinemia, and delayed growth and maturation, was not justified based on available data.

-Finally, they argued that, although the dose/responses relationship for efficacy was admittedly not understood, dosing in current practice for this disorder is more aggressive than that proposed for labeling based on the available data from these trials.

-FDA agreed with many of these arguments and encouraged the sponsor to submit a response to the NA letter. However, we did ask that they try to apply approaches developed by Sheiner, et al, to try to better understand the dose response relationship from the available data. We also asked for additional safety information.

The sponsor responded to the 5-19-05 NA letter in a 1-16-06 submission that included responses to all of our requests. This was reviewed by the clinical group, pharm/tox, and biopharm.

-Andre Jackson, Ph.D., from OCP reviewed the sponsor's attempt to apply a Sheiner approach to the efficacy data. His major concern was that the studies in question (USA-150 and CAN-23) were not conducted in a manner required to apply the Sheiner approach. Thus, the results are not interpretable and still do not provide support for the proposed starting dose and the need for titration. He and the biopharm group conclude that a phase 4 fixed dose study is still needed, e.g., placebo, 0.125 mg and 1 mg.

-The pharm/tox group (Drs. Elayan and Rosloff) conclude that the juvenile rat study will need to be repeated because the high dose was not adequate (they recommend 2.5 mg/kg as the high dose). They also recommend that we ask for a juvenile dog study. They agreed that these studies could be conducted in phase 4.

-Drs. Cai and Khin also agree that the supplement is approvable, but have a number of recommendations for additional data requests and for a phase 4 commitment to conduct a fixed dose study to better establish the lowest effective dose and a need for titration.

CONCLUSIONS AND RECOMMENDATIONS

I agree with the review team that the sponsor has still not adequately established an optimal starting dose and adequately justified a need for titration to higher doses. However, I also agree that additional data to address these questions could reasonably be submitted following approval of this supplement (b) (4). A major justification, as noted, is that current prescribing practice for this indication is even more aggressive than that proposed in this supplement. There are several labeling issues that need to be resolved prior to final approval, and these will likely require some discussion with the sponsor. In addition, we have several requests for clarification and further information that need to be addressed prior to final approval. Thus, I will issue an approvable letter with our proposed labeling, along with our requests for additional data and a commitment to conduct a fixed dose study post-approval.

cc:
Orig NDAs 20-272/S-036, 20-588/S-024 and 21-444/S-008
HFD-130/TLaughren/NKhin/JCai/DBates

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/s/

Thomas Laughren
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MEDICAL OFFICER