M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 2, 2012

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

SUBJECT: Recommendation for approval action for new language in labeling regarding the claim for Risperdal (risperidone) for the treatment of irritability in autism

TO: File NDA 20272_S-065
[Note: This overview should be filed with the 10-3-11 original submission of this NDA supplement.]

1.0 BACKGROUND

Risperdal (risperidone) is an atypical antipsychotic that is approved for the treatment of schizophrenia, bipolar disorder, and the irritability of autism. The program supporting this application, conducted under IND 31,931, was in response to a PMC for the 10-6-06 approval of Risperdal for the irritability of autism. This original approval was based on 2 studies using a flexible dose range (0.25 to 3.5 mg/day), and the recommended dose range is 0.5 to 3 mg/day. We asked them to conduct an additional fixed dose study to explore the lower end of the dose response curve. The sponsor conducted study RIS-AUT-4002 to fulfill this commitment.

2.0 CHEMISTRY

No new CMC data were submitted as part of this application.

3.0 PHARMACOLOGY

No new pharm/tox data were submitted as part of this application, however, there were some changes to certain sections of labeling as part of the review of this application.

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4.0 BIOPHARMACEUTICS

No new biopharmaceutics data were submitted as part of this application, however, there were some changes to certain sections of labeling as part of the review of this application.

5.0 CLINICAL DATA

5.1 Efficacy Data

As noted, a single additional study was done in support of this application, i.e., study RIS-AUT-4002. This was a 6-week, randomized, double-blind, placebo-controlled, fixed-dose (weight-based) study in 96 patients (ages 5-17) with irritability and other behavioral disturbances associated with autism. The 2 dose groups were high (1.25 mg/day for < 45 kg and 1.75 mg/day for > 45 kg) and low (0.125 mg/day for < 45 kg and 0.175 mg/day for > 45 kg). The primary endpoint was change from baseline in the ABC-Irritability subscale of the ABC. Patient completion was high (about 80%), and the high dose group significantly favored risperidone over placebo (-7.9 for drug vs -3.5 for placebo; $p < 0.001$). The low dose group was actually numerically slightly worse than placebo (-3.0 for drug vs -3.5 for placebo). These data were reviewed by Dr. Levin from the clinical group and Dr. Jhong from the biometrics group. Both agreed that this study supports the sponsor's conclusion that the high dose group was shown to be effective, while the low dose group was not, and I do as well.

5.2 Safety Data

The safety data for this NDA were derived from the single 6-week controlled trial and an open-label extension. There were no unexpected findings and no new findings of concern. As part of the PMC, we asked for data on fasting glucose, fasting insulin, insulin growth factor-1, growth hormone, and insulin resistance parameters, and the sponsor collected such data in their program. Dr. Yanoff from DMEP reviewed the glucose data and concluded that the available data did not reveal any negative impact on glucose metabolism, but were quite limited. Dr. Mohamadi from DMEP reviewed the endocrine data and also concluded that the available data did not reveal any negative impact on endocrine parameters, but, again, felt that the data were quite limited. Neither viewed these findings as being sufficiently informative to add any information to labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have now reached final agreement with the sponsor on labeling.

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6.0 LABELING AND APPROVAL LETTER

6.1 Labeling

As noted, we have now reached final agreement with the sponsor on labeling.

6.2 AP Letter

The AP letter includes the agreed upon final labeling.

7.0 CONCLUSIONS AND RECOMMENDATIONS

I agree with Dr. Levin that this application fulfills the PMC and supports the changes to labeling regarding the dose response findings for efficacy in the irritability of autism. There were no new important safety findings, and we have reached final agreement with the sponsor on labeling. Thus, we will issue an approval letter with the agreed upon final label.

cc:
Orig NDA 20272_S-065
HFD-130
HFD-130/TLaughren/MMathis/RLevin/ASohn

DOC: Risperdal_Autism_Laughren_AP_Memo.doc

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

/s/

THOMAS P LAUGHREN
08/02/2012