CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Pharmacology Review(s)

Pregnancy Category SLR-017

PHARMACOLOGY/TOXICOLOGY MEMORANDUM TO NDA **20-272**

Date: 9/17/02
Reviewer: Lois M. Freed, Ph.D.
Drug: Risperdal
Sponsor: Janssen Pharmaceuticals
Indication: schizophrenia
Re: Submission SLR-017 [dated: 5/29/02]

SLR-017

The sponsor requested revision of labeling proposed by the Agency [FDA letter, 7/19/01] as noted in **bold** in the attached document [i.e., J&JPRD Counterproposal].

Reviewer comments: it is recommended that the phrase, ". [redacted] ' not be added to labeling. The purpose of the cross-fostering study was to assess the contribution of direct fetal and maternal effects on findings observed in the original reproduction studies. The results of the cross-fostering study, including effects on the dams, are described in labeling. Therefore, the revision proposed by the sponsor is unnecessary and, more importantly, could be considered to overemphasize maternal effects.

In order to update (and clarify) labeling, the following changes are recommended:

PREGNANCY CATEGORY C:

2 pages redacted from this section of the approval package consisted of draft labeling

Carbamazepine SLR-018

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-272/SLR-018 20-588/SLR-012	Submission Date: May 29, 2002
Name of Drug:	Risperdal® (risperidone) Tablets (0.25, 0.5, 1, 2, 3, and 4 mg), oral solution (1 mg/mL)	
Indication of Drug:	Treatment of psychotic disorders (schizophrenia)	
Sponsor:	Janssen Research Foundation	
Type of Submission:	Amendment to Labeling Supplement	
Reviewer:	Maria Sunzel, Ph.D.	

Review of the sponsor's counterproposal of the label revision for Risperdal® (risperidone) - PRECAUTIONS: Drug-Drug Interactions (risperidone - carbamazepine).

The label revision of the drug-drug interaction with carbamazepine and risperidone was evaluated by the Agency in 2001 and the sponsor received an approvable letter on November 5, 2001 (OCPB review dated 10/02/01). The sponsor has now submitted an amendment and proposes minor revisions in the Agency's proposal of the PRECAUTIONS: Drug-Drug Interactions Subsection for risperidone (Risperdal®) tablets (NDA 20-272) regarding the drug-drug interaction with carbamazepine. This submission is cross-referenced to NDA 20-588 (Risperdal oral solution). The office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds some of the sponsor's revisions acceptable, and only proposes minor revisions to the sponsor's counter-proposal.

The sponsor proposes the following revision of the text proposed by the Agency on 11/05/01 (changed text marked in bold, deletions as strike-through text):

OCPB concurs with the sponsor's proposal to combine the label text regarding initiation and cessation of carbamazepine therapy (with a clarification that the initiation and cessation refers to carbamazepine). The sponsor proposes a deletion of the specific drugs that are known — inducers, with the rationale that risperidone is metabolized via CYP2D6, and that the minor metabolic contribution of — (*in vitro* estimate of 10-15%) is not mentioned in the label. Therefore, the sponsor indicates that the statement regarding specific drugs may be confusing for the prescriber. We do not fully agree, but since it is reported that carbamazepine induces other CYP isozymes, we propose a deletion of — (replaced by 'enzyme') since an induction of solely — is unlikely to be the sole induced pathway to the observed *in vivo* interaction

between carbamazepine and risperidone. However, we recommend that the list of specific drug examples is retained to guide the prescriber (with the exception of St John's Wort which is reported to be a specific — inducer). In addition, we recommend the retention of precautionary text that the efficacy of risperidone may be reduced during concomitant therapy with enzyme inducers.

OCPB proposes the following revision of the text the sponsor's amended label text (changed text marked in bold, deletions as strike-through text):
PRECAUTIONS: Drug Interactions

Recommendation:
The amended proposed label revision for Risperdal® (risperidone) tablets is not fully satisfactory to the Office of Clinical Pharmacology and Biopharmaceutics. Please convey the suggested revision of the proposed, amended label text to the medical reviewer.

Maria Sunzel, Ph.D. /S/

RD FT Initialed by Ramana Uppoor, Ph.D. /S/

cc: NDA 20-272, NDA 20-588, HFD-120 (Hardeman, Mosholder, Hearst, Laughren), HFD-860 (Mehta, Uppoor, Sunzel)

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/s/

Maria Sunzel
7/1/02 11:26:09 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/1/02 12:19:34 PM
BIOPHARMACEUTICS