CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-346

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA:	21-346
Sponsor:	Janssen
Clock Date:	8/31/01

Drug Name

Generic Name	Risperidone Long Acting Injection
Trade Name	Risperdal CONSTA

Drug Characterization

Pharmacological Category:	Benzisoxazole derivative
Proposed Indication:	Schizophrenia
NDA Classification:	3-S
Dosage Forms, Strengths, and Routes of Administration:	Injection 25mg, 37.5mg and 50mg

Reviewer Information
Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 10/01/03

EXECUTIVE SUMMARY:

The sponsor has provided a summary of published and unpublished literature that makes a persuasive case for the usefulness and need of Risperdal Consta. The safety data updated in this submission is similar to that of the original NDA for Risperdal Consta. No new pattern of events was uncovered that would alter the risk/benefit profile of Risperdal Consta as pesented in the original NDA. From a clinical viewpoint I recommend that Risperdal Consta be approved.

I. REVIEW:

BACKGROUND

Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), submitted a New Drug Application for RISPERDAL CONSTA (NDA 21-346), a long-acting injection formulation of risperidone, in the treatment of schizophrenia on August 31, 2001.

The Division of Neuropharmacological Drug Products (DNDP) notified J&JPRD on June 28, 2002 that the application for RISPERDAL CONSTA was not approvable under Section 505(d) of the Act and 21 CFR 314.125(b). Three Pharmacology/Toxicology deficiencies were cited in the letter as the primary factors influencing the decision by the Division to not approve NDA 21-346: (1) differences in the tumor profiles in the 24-month carcinogenicity studies with RISPERDAL CONSTA and RISPERDAL tablets; (2) no reproductive toxicology studies with RISPERDAL CONSTA; and (3) no data to support that impurities were qualified in the oral nonclinical studies. The Division elaborated further by concluding, "These findings would preclude approval of this application in the absence of any demonstration of a clinical advantage of this product".

J&JPRD met with DNDP on July 26, 2002 to discuss plans to address each of the pharmacology/toxicology issues cited in the Action Letter and to initiate discussion regarding the clinical benefit of RISPERDAL CONSTA J&JPRD again met with DNDP on February 25, 2003 to discuss plans for the complete response to the Action Letter. Three main topics were discussed at the meeting: (1) the potential clinical benefit of a long-acting intramuscular (IM) formulation of an atypical antipsychotic; (2) nonclinical studies that would be submitted in the complete response to address pharmacology/toxicology issues raised in the Action Letter; and (3) plans to conduct an embryofetal toxicity study with RISPERDAL CONSTA.

Following a presentation of the potential clinical benefit of RISPERDAL CONSTA, the Division agreed that there is a potential clinical benefit of a depot atypical antipsychotic and suggested that the complete response should contain a detailed review of the existing data for IM depot and oral formulations that make a compelling argument for improved compliance and

decreased relapse of psychotic symptoms with depot antipsychotics. The Division further agreed to consider approving RISPERDAL CONSTA without a complete resolution of the carcinogenicity findings in rat if the data demonstrate that the IM depot formulation provides clinical benefit. J&JPRD provided a list of nonclinical studies that would be included in the complete response to address the pharmacology/toxicology deficiencies cited in the Action Letter. In addition to these studies, the Division requested summary and individual data listings for the incidence of adrenomedullary findings (including adrenal pheochromocytoma) from the oral carcinogenicity study in rat. The Division noted that if J&JPRD proposed strain or substrain differences as an explanation for the differences in tumor profiles between the oral and IM depot studies, it would be important to provide data by which to compare the relevance of each strain or substrain for assessing human risk.

At the February 25, 2003 meeting, the Division stated their position that the complete study report for the IM depot embryofetal developmental toxicity study should be submitted to NDA 21-346 prior to approval. However, the Division agreed to consider the potential for a clinical benefit when making a decision as to the need for the embryofetal developmental toxicity study prior to approval. The Division further agreed to continue discussions related to the design of the embryofetal toxicity study at a later time.

At a teleconference held on March 25, 2003 with J&JPRD and Dr. Lois Freed, Pharmacology/Toxicology Reviewer for DNDP, the following agreements were reached on the design of the embryofetal toxicity study:

•Dr. Freed agreed that the 80 mg/kg dose was too high because it impairs mating, and suggested that J&JPRD consider a dose between 20 mg/kg and 80 mg/kg. An additional dose-ranging study will be conducted to evaluate possible higher doses than 20 mg/kg.

•A third dose (below 20 mg/kg) group will be added to the study.

•An oral treatment group is required to provide a reference to the previous study with RISPERDAL tablets (NDA 20-272). In addition to agreements reached on the design of the study, J&JPRD agreed to include a proposal in the complete response regarding the timing of the submission of the embryofetal toxicity study.

Organization of the Response to the Action Letter

This document contains the responses from J&JPRD to issues identified by DNDP in the Action Letter, dated June 29, 2002, for RISPERDAL CONSTA, (NDA 21-346, submitted August 31, 2001). The organization

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