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Sent:	Friday, August 07, 2009 10:51 AM
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Subject:	Submission to NIOSH Docket on Hazardous Drug Listing: Risperidone
Attachments:	Submission to NIOSH Docket on Hazardous Drug Listing_Risperidone (2).doc

Message sent on behalf of Ellen Faria, Johnson & Johnson Occupational Toxicologist

NIOSH Docket Office, Barbara and Tom,

Please consider the attached document for review:

<<Submission to NIOSH Docket on Hazardous Drug Listing_Risperidone (2).doc>>

If you have questions or concerns, please feel free to contact Ellen Faria via email efaria1@its.jnj.com or cell 908-623-7472.

Johnson & Johnson

To: NIOSH Docket Office

From: Ellen C. Faria, Ph.D., DABT

Ref: Regulatory Submittal to the National Institute for Occupational Safety and Health (NIOSH) to request that Risperidone (CAS #: 106266-06-2) be considered a non-hazardous drug and excluded from the 'Hazardous Drug Alert List'

The critical importance of assuring the identification of hazardous drugs and products used in health care settings, and the provision of detailed guidelines for the handling of such products is recognized. Also of importance is the need for a robust process for the identification of hazardous active pharmaceutical ingredients (APIs) and products, to assure the usefulness and applicability of listings of APIs and products considered hazardous. The purpose of this communication is to outline considerations regarding the proposed inclusion of risperidone in the listing of APIs fitting the NIOSH criteria for hazardous drugs. For the reasons outlined within this document, Johnson & Johnson (J&J) believes that risperidone does not meet the criteria for listing as a hazardous drug. With a view to assuring the accuracy and appropriateness of the final published listing of APIs and products considered hazardous, an overview of the relevant scientific data is provided to support the conclusion that risperidone does not fit the criteria for a hazardous drug.

EXECUTIVE SUMMARY

Risperidone (Respirdal®) has been proposed by NIOSH as a hazardous drug, to be added to a list of hazardous drugs previously published in the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings 2004 (NIOSH Alert, 2004).

J&J does not feel that existing scientific data support the listing of risperidone as a hazardous drug because of the following:

- Risperidone does not meet the primary toxicity characteristics of hazardous drugs as described in the NIOSH Alert (2004). It is not considered to be teratogenic or a developmental toxin, cause effects on fertility, or is genototoxic. The data is inconclusive at this time in terms of carcinogenic potential. It does not produce serious organ toxicity. These toxicity criteria are the primary reason and purpose for the handling of hazardous drugs more carefully in health care settings and risperidone does not meet these criteria.
- Risperidone does not have most if not all of the toxicity characteristics in common with the compounds currently listed which are almost exclusively cytotoxic anticancer drugs and sex steroid hormones.
- The potential for exposure to health care workers is reduced by the dosage form of risperidone. The NIOSH Alert (2004) describes conditions for exposure in the handling of hazardous materials, with a focus on handling of liquid, powdered or lyophilized drugs where spills or inhalation may contribute to accidental exposure. With respect to solid oral dosage forms, specific concern is noted for handling of uncoated tablets, whereas the primary dosage form for Risperdal® is a coated tablet and as such exposure through handling is minimized.

- Although the starting therapeutic dose is low and within the criteria for a potent compound according to the NIOSH criteria, this dose is based on the potential pharmacological effect rather than toxicological effects. In other words, it is designed to cause minor and reversible pharmacological changes and therefore is not considered a "serious" effect under the NIOSH definition.

The scientific data summarized within this document supports that risperidone does not meet the criteria established by NIOSH for a "hazardous drug". J&J requests that NIOSH not list this with other much more significantly potent and toxic drugs in the NIOSH Alert so that adequate precautions be applied to hazards of appropriate concern to health care workers. The following provides further scientific evidence to support that risperidone not be listed.

INTRODUCTION

The NIOSH criteria for defining a hazardous drug is the following (NIOSH Alert, 2004):

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity [††]
3. Reproductive toxicity [††]
4. Organ toxicity at low doses [††]
5. Genotoxicity [‡‡]
6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

[††]All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 $\mu g/m^3$ after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

The following summaries the clinical and non-clinical data for risperidone and determine its applicability to the NIOSH definition of a "hazardous drug" described above.

SUMMARY OF HUMAN AND NON-CLINICAL TOXICITY DATA

Therapeutic Indication and Dose

Risperidone is indicated for the treatment of psychotic disorders, including schizophrenia (AHFS, 2004). Although starting doses may be as low as 1 mg/day, the recommended daily dose by oral administration is 2-8 mg (PDR, 2009). The maximum recommended daily dose is 16 mg (Martindale, 2009). The drug may also be administered by intramuscular injection, at a dosage of 25-50 mg once every two weeks. Although the dose is within the NIOSH criteria, its maximum dose is higher, and is intended to cause minor rather than "serious" effects toxicologically.

Pharmacological Mechanism of Action

Risperidone is an atypical antipsychotic agent (AHFS, 2009). The mechanism of action has not been well characterized. However, it has been proposed that the drug acts as a selective dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) receptor antagonist (PDR, 2009; Martindale, 2009). Antagonism of other receptor types may explain some of the other effects of risperidone. J&J feels this mechanism of action is not consistent with of any of the listed compounds in the NIOSH Hazard Alert (2004), which are primarily cytotoxic oncolytic compounds and sex steroid hormones.

Pharmacokinetics

Risperidone is well absorbed (~70%) by the oral route (PDR, 2009). After oral administration, peak plasma concentrations are achieved in 1-2 hours (Martindale, 2009), and steady-state concentrations in 1-5 days (PDR, 2009). The drug is extensively metabolized by the liver, and is excreted primarily in the urine. One metabolite, 9-hydroxyrisperidone (paliperidone; the active metabolite), has pharmacological activity similar to that of the parent drug. The enzyme that metabolizes risperidone exhibits a genetic polymorphism: in those who are "extensive metabolizers," the elimination half-lives of the parent drug and active metabolite are 3 and 21 hours, respectively, while in those who are "poor metabolizers," (6-8% of the Caucasian population) the elimination half-lives are 20 and 30 hours, respectively (Martindale, 2009; Meditext, 2009). No information was identified on inhalation pharmacokinetics.

Clinical/Human Health Effects Summary

The most commonly reported adverse effects involve the nervous (agitation, anxiety, dizziness, involuntary movements, tremors, and somnolence), gastrointestinal (upset stomach, constipation, and nausea), respiratory (runny nose), and cardiovascular (orthostatic hypotension and increased heart rate) systems (AHFS, 2009; PDR, 2009). Most if not all of these clinical effects from oral exposure clinically are mild to moderate, and are reversible upon cessation of treatment, i.e., would not be considered serious (PDR, 2009).

As with other dopamine D_2 antagonists, risperidone may also increase prolactin secretion (Martindale, 2009). This may result after long-term chronic administration in sexual disturbances in men. These may include reduced libido, ejaculatory difficulties, erectile dysfunction, gynecomastia (development of breasts in males) and impaired orgasm, while in women increased prolactin secretion after chronic administration of the drug may include menstrual irregularities, reduced libido, impaired orgasm and decreased vaginal lubrication (Baggaley, 2008, Reprotox, 2005).

Non-Clinical/Animal Toxicology Summary

Acute/Short-term studies – The acute oral LD_{50} in rats and mice was approximately 60 mg/kg; the intravenous LD_{50} in rats and mice was approximately 30 mg/kg (RTECS, 2009).

Long-term studies (>28 days) – In repeat-dose oral toxicity studies in rats and dogs of up to 12 months, the primary effects observed with exposure to risperidone included hematological changes, prolactin-mediated mammary gland stimulation, central nervous system effects related to the pharmacological action of the drug and decreases in

testes/prostate weight (EMC, 2007; Janssen-Ortho, 2007). Lowest-observed-effect-levels (LOELs) in 12-month repeat dose toxicity studies were <10 mg/kg/day and <0.31 mg/kg/day in rats and dogs, respectively.

Reproductive toxicity (fertility impairment) – Mating, but not fertility, was impaired in rats given risperidone orally at 0.16 to 5 mg/kg/day (PDR, 2009). This impairment was thought to occur only in female animals, as a follow-up study in which only males were treated was negative. In dogs given risperidone orally at 0.31 to 5 mg/kg/day, sperm motility, sperm concentration, and testosterone were decreased.

Developmental toxicity (birth defects) – Risperidone was negative for birth defects in rats and rabbits at oral doses of 0.63-10 and 0.31-5 mg/kg/day, respectively (PDR, 2009). Additionally, impaired learning was found in adult offspring of pregnant rats that had been treated with 3 times the maximum human dose of risperidone (TERIS, 2009; Shepards, 2009). Although increased fetal death was observed in rats, this effect may have been secondary to maternal toxicity.

Genotoxicity – Risperidone was negative in the Ames bacterial mutagenicity assay, an *in vitro* rat hepatocyte DNA-repair assay, a mouse lymphoma mutation assay, chromosomal aberration tests in human lymphocytes and Chinese hamster cells, the sex-linked recessive lethal test in *Drosophila* and an *in vivo* mouse micronucleus test (PDR, 2009).

Carcinogenicity – Although risperidone was positive for several endocrine-related cancers in long-term studies in mice and rats dosed orally at 0.63-10 mg/kg/day, these types of cancers are considered related to increased prolactin secretion. Rodents may be more susceptible to some prolactin-mediated tumors than humans, and consequently, the clinical relevance of this finding is unclear (PDR, 2009). Clinical and epidemiological studies to date have not shown any link between chronic use of these drugs and an increased risk of tumors. Therefore, it is considered to be inconclusive for risperidone to be considered carcinogenic.

RATIONALE FOR NOT LISTING RISPERIDONE ON NIOSH HAZARDOUS DRUG ALERT LIST

As described above, risperidone from oral administration of primarily coated tablets may have some significant clinical effects. However, and most importantly in the context of its listing as a hazardous drug by NIOSH, it has the following properties that would not list it with the other compounds currently listed.

- Risperidone does not meet the primary toxicity characteristics of hazardous drugs as described in the NIOSH Alert (2004). It is not considered to be teratogenic or a developmental toxin, cause effects on fertility, or be genototoxic. The data is inconclusive at this time in terms of carcinogenic potential. It does not produce serious organ toxicity. These toxicity criteria are the primary reason and purpose for the handling of hazardous drugs more carefully in health care settings and risperidone does not meet these criteria.

- Risperidone does not have most if not all of the toxicity characteristics in common with the compounds currently listed which are almost exclusively cytotoxic anticancer drugs and sex steroid hormones.
- The potential for exposure to health care workers is reduced by the dosage form of the drug. The NIOSH Alert (2004) describes conditions for exposure in the handling of hazardous materials, with a focus on handling of liquid, powdered or lyophilized drugs where spills or inhalation may contribute to accidental exposure. With respect to solid oral dosage forms, specific concern is noted for handling of uncoated tablets, lyophilized powders, etc. whereas the primary dosage form for Risperdal® is a coated tablet and as such exposure through handling is minimized. The activities involved in the administration of Risperdal® do not overexpose health care workers and does not put them at increased risk.

Based on the existing data reported, we ask that you consider exclusion of risperidone from the NIOSH Hazardous Drug List. Thank you for your time and consideration.

Regards,

Ellen C. Faria, PhD DABT
Principal Occupational Toxicology
Chair, Pharma Occupational Toxicology Advisory Committee
GPSG
Johnson & Johnson

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