

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-346

CORRESPONDENCE

Hardeman, Steven D

om: Hardeman, Steven D
Sent: Tuesday, October 28, 2003 1:53 PM
To: Claude McGowan Ph. D. (CMcgowan@JANUS.JNJ.com)
Subject: Risperdal Consta Labeling and Phase IV Commitments

Claude,

If we go to a final action tomorrow (and it looks like we will), we will need for you commit to some phase IV studies:

We request that you commit to the following (Phase IV):

Further investigate the osteodystrophy observed in the 1-year i.m. depot toxicity and the 2-year i.m. depot carcinogenicity studies in rat. Additional studies to be conducted Phase 4 should address the exact nature of the bone lesion(s) and possible mechanism(s) underlying this finding

Conduct an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma assay (with colony sizing) to assess the genotoxic potential of the process impurity, _____. The study can either be conducted using a drug batch enriched in _____ or directly testing _____

Conduct an i.m. depot embryofetal development study in rats. (I think you're already doing this - but it has to be in the final action letter)

For each of the above, I need for you to give me three dates:

1. Protocol Submission
2. Study Start
3. Final Report Submission

Once I get agreement on the commitments and dates from both sides, plus the final agreed-upon labeling, I will finalize a letter.

Thanks,
Steve

CAPT Steven D. Hardeman, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

Phone: 301-594-5525
Fax: 301-594-2859

10/29/03

PHASE IV COMMITMENTS FOR RISPERDAL® CONSTA™

Per FDA's request, we commit to conducting the following Phase IV studies. We are also providing, as requested, time estimates for protocol submission, study start and final report submission for each study.

Further investigate the osteodystrophy observed in the 1-year i.m. depot toxicity and the 2-year i.m. depot carcinogenicity studies in rat. Additional studies to be conducted Phase 4 should address the exact nature of the bone lesion(s) and possible mechanism(s) underlying this finding.

1. Protocol Submission: within 3 months after receipt of the letter
2. Study Start: within 6 months after receipt of the letter
3. Final Report Submission: within 30 months after receipt of the letter

Conduct an in vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma assay (with colony sizing) to assess the genotoxic potential of the process impurity, _____ The study can either be conducted using a drug batch enriched in _____ or directly testing _____

1. Protocol Submission: within 3 months after receipt of the letter
2. Study Start: within 5 months after receipt of the letter
3. Final Report Submission: within 8 months after receipt of the letter

Conduct an i.m. depot embryofetal development study in rats. (I think you're already doing this - but it has to be in the final action letter):

1. Protocol Submission: protocol was submitted
2. Study Start: study has started
3. Final Report Submission: within 2 months after receipt of the letter

APPROVED FOR SIGNATURE
DATE

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



NDA 21-346

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) dated August 31, 2001, received August 31, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Risperdal Consta (risperidone) Long-Acting Injection.

We also acknowledge receipt of your submissions as follows:

September 19, 2001	October 15, 2001	October 24, 2001	December 4, 2001
December 10, 2001	December 19, 2001	March 1, 2002	March 25, 2002
March 29, 2002 (3)	April 5, 2002	April 30, 2002	May 29, 2002
June 6, 2002	June 14, 2002	June 18, 2002	

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Pharmacology / Toxicology

1. The tumor profile in the 2-yr intramuscular (IM) depot carcinogenicity study in rat was different than that observed in the 2-yr oral studies in mouse and rat [NDA 20-272, RISPERDAL tablets]. Two tumor types, renal tubular adenomas and adrenomedullary tumors, were observed only with the IM depot formulation. This raises the concern that the IM depot formulation may be more tumorigenic than oral risperidone. You concluded that the renal tubular adenomas and adrenomedullary tumors were related to elevations in serum prolactin. However, the information/data provided did not support this mechanism. For example, there was not convincing evidence of an exacerbation of chronic renal disease in high-dose males, either as a group or in the individual animals with renal tubular adenomas. In addition, the mechanistic studies conducted in rats did not provide adequate data for dismissing the possibility of a unique tumor profile [with the IM depot formulation] on the basis of substrain differences or differential effects of route on serum prolactin. When serum prolactin effects were assessed following oral and IM depot administration, the AUC for serum prolactin was greater following oral dosing. This finding undermines the view that elevated prolactin is primarily responsible for the tumors seen with IM dosing.

The data from the genotoxicity studies indicate that risperidone is not genotoxic; therefore, there is a presumed threshold for tumorigenic effects. However, in the IM depot study, there was no safety margin between plasma exposures at the no-effect doses for renal and adrenomedullary tumors and that expected at the maximum recommended clinical dose.

These findings would preclude approval of this application in the absence of any demonstration of a clinical advantage of this product. Of course, if you have additional data or information that would support the conclusion that the renal tubular adenomas and adrenomedullary tumors are irrelevant in terms of human risk, such data/information should be submitted for review.

2. No reproductive toxicology studies were conducted using the IM depot formulation of risperidone. The reproductive toxicology studies conducted using oral risperidone were used to support the IM depot formulation. Findings observed in the 1-yr chronic and the 2-yr carcinogenicity studies in rat using the IM depot formulation suggest that the IM depot formulation may have different toxicities than the oral formulations [for which a complete battery of reproduction studies was conducted]. Specifically, the osteodystrophy detected in the 1-yr and 2-yr studies and the additional tumor types observed with the IM depot formulation raise a concern that the oral reproductive toxicity studies may not provide an adequate test of the potential for the risperidone IM depot formulation to produce reproductive toxicity. It is recommended that, at a minimum, you conduct an embryofetal development study in rat using the clinical IM depot formulation. It is further recommended that an oral dose group be included in the study.
3. You reported that — impurities are present in the risperidone IM depot formulation that are not present in the oral formulations [i.e., tablet, oral solution]. It was stated that impurity — was qualified in oral nonclinical studies; however, documentation to support this statement was not provided. — impurities — were considered to be qualified on the basis that they are rapidly converted to the parent compound when administered. Adequate data were provided to support this statement relative to impurity — however, no data were provided for — Therefore, additional data are needed to address these deficiencies.

We have the following requests and comments unrelated to the not approvable deficiencies, and which should be addressed should you wish to re-submit your application:

Chemistry, Manufacturing and Controls

- 1) Please note that only the Janssen County Cork, Ireland site should manufacture the drug substance for Risperdal Consta since only the Ireland facility was submitted for this NDA.
- 2) A re-test date of — is granted for the drug substance risperidone based on the stability data provided in DMF —
- 3)

4)

5) The only individual specified impurity common to oral and IM formulation is _____
Please clarify the following for the individual specified impurities:

- a) Are impurities _____ qualified through toxicological studies and if so, when?
- b) Based on extensive release and stability data from _____ scale / _____, and _____ commercial scale _____ batches, please adopt the following specifications for the individual specified impurities: _____

These acceptance criteria for these three individual impurities are consistent with the ICH guidelines and based on the extensive release and stability data provided.

6) The specifications for _____ are higher than the _____ recommendation of NMT _____ unless justified by manufacturing capabilities. The higher than _____, specification for _____ should be justified based on documented attempts to lower the levels of _____ during manufacturing. In the absence of such a justification, please comply with the _____ recommendation of NMT _____ specification for _____

7) Please provide information on components and composition of the SmartSite device. Also, please provide data on _____ to support use of the SmartSite device with reconstituted Risperdal Consta for a maximum of _____ as per instructions on the package insert.

8) Please continue to monitor for particle size as part of the stability protocol since a significant amount of data to support its elimination is not available from stability studies.

9) Please incorporate all the regulatory specifications for the first three full-scale production batches and future lots for the microspheres and diluent. Reduced testing for annual stability lots is not acceptable. Please perform testing at all time points for the annual stability lots. In addition, annual lots on stability should include one lot of the commercial kit of each strength.

10) An expiration date of 24 months is granted for the risperidone microspheres and diluent.

11) Although we are not, in general, commenting on your proposed labeling, we note that in your proposed HOW SUPPLIED section of the label and on the carton label, it states that the dose pack should be protected from light. The primary stability data provided in the NDA do not indicate any need for protection from light. Please justify your proposed statement.

Clinical Pharmacology and Biopharmaceutics

- 1) **Phase IV commitment:** The proposed regulatory in vitro dissolution methods are acceptable. However, we recommend that the proposed in vitro release specifications be used only during an interim period, until data are available from the on-going stability tests on the dosage strengths of the to-be-marketed Risperdal Consta products (25°C/60% RH & 5°C conditions). As a Phase IV commitment, we request that you submit the in vitro release data from the on-going stability tests on validation lots of all strengths within 4 months after the 24-month stability data is available, together with a proposal of the final in vitro release specifications based on this data. This proposal should also include release specifications for individual samples, in addition to the specifications of the means. We also request that you clarify the acceptance criteria for the release of batches if an 'out-of-trend' result was obtained, i.e. what actions are taken if re-testing shows consistent out-of-trend results for individual samples.
- 2) For the interim specifications, we propose one revision (a tightening of the T50% time-point) to the specification of the means, and also inclusion of formal specifications for individual samples (+ or ± 10% of the value). We recommend the following revisions (marked in bold) regarding the mean (T50% 45°C water bath) and the inclusion of formal limits for individual samples in the specifications:

Test method* (medium pH 7.4)	Test point	Specification (mean)	Specification## (individual sample)
<i>In vitro</i> release (37°C water bath)	Day 1 Day 15	/	/
<i>In vitro</i> release (45°C water bath)	T _{50%} Day 8		
* Samples tested in triplicate; **Proposed by the sponsor, ##All individual samples should meet this criteria			

3) **Population pharmacokinetic analysis:** Data sets submitted to the FDA were different from those you used in the population pharmacokinetic analysis. One combined file, which consisted of data from all of the three Phase III trials, was used. However, the files submitted to the Agency were data for each study. No control streams were submitted. In order for the Agency to evaluate the appropriateness of your analysis, exact control streams as well as data sets with identically matching file names should be submitted in all future submissions. In addition, the individual two-stage analysis was not documented at all – only final results were displayed. Lack of submission of appropriate documentation of the analysis can lead to duplication of efforts, burdensome reanalysis, and suboptimal use of resources.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
6/28/02 11:18:51 AM



NDA 21346

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O.Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Risperdal Consta (risperidone) Long-Acting Injection

Review Priority Classification: Standard (S)

Date of Application: August 31, 2001

Date of Receipt: August 31, 2001

Our Reference Number: NDA 21346

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 30, 2002 and the secondary user fee goal date will be August 31, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Steve Hardeman
11/2/01 09:39:24 AM
Signed for John Purvis

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OR ORIGINAL