Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560

16 AUG 2005

Thomas P. Laughren, M.D.
Acting Director
Division of Psychiatry Products
Center for Drug Evaluation and Research (HFD-130)
Food and Drug Administration
Attn: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 20-272/S-036
RISPERDAL® (risperidone) Tablets

Cross Reference:
NDA 20-588/S-024 for RISPERDAL® (risperidone) Tablets Oral Solution and NDA 21-444/S-008 for RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets

RESPONSE TO FDA ACTION LETTER FOR AUTISM AND REQUEST FOR MEETING

Dear Dr. Laughren,

Reference is made to the Agency's Not Approvable Letter, issued 19 May 2005 to Johnson & Johnson Pharmaceutical Research & Development (J&JPRD, the Company) for supplemental New Drug Application (sNDA) 20-272/S-036 (cross-referenced to NDA 20-588/S-024 and NDA 21-444/S-008) for RISPERDAL (risperidone) in the treatment of irritability associated with autism. Reference is also made to the sNDA submission of 19 December 2003, the Agency's Approvable Letter of 18 June 2004, the complete response filed on 18 November 2004 pertaining to RISPERDAL (risperidone) in the treatment of irritability associated with autism, and the 27 May 2005 response stating the Company's intention to file an amendment to the application in response to the Agency's most recent Action Letter.

The Company has reviewed the 19 May 2005 Not Approvable Letter in depth, with close attention to all the safety issues and concerns that have been raised by the FDA, and strongly disagrees with the Division's assessment of the autism dossier. In the Company's opinion, it can address all issues raised in the Not Approvable Letter in a reasonable manner, as reflected here and further elaborated in the accompanying support document.

The Company respectfully requests a meeting with the Division and Dr. Robert Temple to further discuss and resolve the Agency's issues from the 19 May 2005 Action letter such that agreement can be reached for the approval of risperidone for the treatment of irritability associated with autism. Reference is made to a brief conversation that took place on 1 June 2005 between Dr. Temple and Dr. Bonnie Goldmann, J&JPRD Global Regulatory Affairs. In that conversation, Dr. Goldmann

PRD-1C

communicated the position of J&JPRD relative to the 19 May 2005 Not Approvable action and indicated that the Company had serious concerns with that action. Dr. Temple indicated that the Company should formally respond to the Division with our concerns, but that he would become involved with the Division in helping to resolve this issue. With the recent restructuring of the Division of Neuropharmacologic Drug Products, the enclosed communication is provided to your attention with the request that Dr. Temple continue to work with the Division and the Company on this issue. Additional information and responses to the Division's most recent action are provided with this communication for your reference. It is anticipated that this information will provide sufficient information to serve as a background package for the meeting we have requested.

Background to the sNDA Application

Autism is a serious and debilitating neurodevelopmental disorder, with core deficits in communication, socialization and brain processing of stimuli. It is commonly accompanied by a range of severe behavioral symptoms, which cause profound dysfunction and can pose a major challenge for the patient in accessing and responding to appropriate psychosocial and educational treatment. There is a major and significant unmet medical need for this condition, which has no approved medication, often requires life-long supportive care, and may even result in significant periods of institutionalization.

There is a consensus among experts and practitioners in the fields of autism and child psychiatry that risperidone offers major clinical benefit in the treatment of severe and disabling symptoms associated with autism. The clinical importance of this benefit can be profound, since autistic children and adolescents with symptoms in the irritability spectrum are commonly unable to utilize the psychosocial and educational treatments that are essential for managing this condition. Effective treatment with risperidone not only reduces the distress and burden associated with the symptoms, but also allows these patients to become relatively more functional and receptive to other treatment interventions.

Furthermore, because the disorder is relatively uncommon (2 to 5 cases per 10,000 subjects), major challenges exist in studying treatment effectiveness and outcomes in this condition. The children and adolescents affected have no, or at best poor, communication abilities, and often manifest movements, posturing, fidgetiness, agitation, anxiety and unpredictable reactions to new stimuli as inherent signs of autism that are difficult to distinguish from treatment-related adverse events. The efficacy and safety results from the pivotal trials used to support this application should, therefore, be viewed in the context of the seriousness of this disorder, the challenges in studying treatment effectiveness in the patient population, and the benefit/risk of treatment with risperidone.

On 1 April 2003, the Company met with the FDA to discuss efficacy and safety data from two pivotal trials in autism, RIS-USA-150 and RIS-CAN-23, which were provided to the Division in the information package for the pre-NDA meeting. At this meeting, the Division indicated that the sNDA was fileable and reviewable for the

proposed indication, and would undergo a priority review due to the unmet medical need in these patients, given that there are no drugs approved for the treatment of autism. The Division also agreed that the number of patients and the duration of exposure to risperidone were adequate to evaluate the overall safety of risperidone in these patients, and that safety data from trials of disruptive behavior disorders (DBD) in children and adolescents (including long-term trials) were pertinent for the autism application.

The sNDA was submitted to the Division on 19 December 2003 and included data as discussed at the 1 April 2003 pre-NDA meeting. The Company received an Approvable Letter from the FDA (dated 18 June 2004) that highlighted the following key points:

a) The Company has demonstrated the effectiveness of RISPERDAL in the treatment of the irritability associated with autism. However, a substantial number of patients in the trials received doses at or near the maximum dose. Given the flexible dose regimen employed, the FDA could not determine that these larger doses are necessary.
b) The incidences of important adverse events (somnolence, increased appetite, fatigue, EPS, weight gain and constipation) were particularly high and these AEs were likely dose related.
c) In controlled trials, few patients discontinued treatment due to an AE. This does not necessarily mitigate the longer-term risk of AEs, however, and the FDA was concerned about the long-term AEs (tardive dyskinesia, prolactin elevation, weight gain, and tachycardia) that could be dose related.
d) A fixed-dose trial would need to be conducted (perhaps as a phase IV study), to adequately explore the dose response relationship for risperidone in this population. However, to support approval before such a trial is conducted, the FDA would be willing to entertain the possibility that the Company could draft labeling, based on the current data, to ensure that patients received the lowest possible effective dose. Such dosing recommendations might require that patients be started on a low dose and maintained on that dose for a substantial duration in order to ensure that the maximal response to that dose had been observed.

The Company submitted a complete response on 18 November 2004 that, in the opinion of J&JPRD, addressed all of the deficiencies and requests noted in the 18 June 2004 Approvable Letter.

Following the submission of that complete response, the Company received a Not Approvable Letter from the FDA on 19 May 2005 that outlined the following chief concerns:

a) There was an unacceptably high incidence of adverse events even at the lowest doses studied.
b) The coding of events like akathisia and dyskinesia may be inaccurate.
c) There were potential long-term risks.
d) The proposed dosing recommendations would not permit prescribers to reliably identify a dose that is both effective and acceptably safe in any particular patient.

Summary of J&JPRD's Position

The Company considers that the data submitted to the Division demonstrate robust efficacy of risperidone in the treatment of irritability associated with autism and adequately address each of the concerns raised by the Agency for approval of this indication. Specific justifications for our position on each of the Agency's concerns are described in the following sections, with additional elaboration of the available data included in the supporting summary document.

Incidence of Adverse Events in Children and Adolescents with Autism

The Company has carefully studied the FDA's concern over the safety of risperidone in young people with autism. Based on a thorough review of the data, J&JPRD's concludes that the adverse events in children and adolescents with autism were largely mild to moderate and/or transient, and very few (1.3%) patients discontinued from the trials due to adverse events. Overall, there were no adverse events seen with risperidone use in autistic children and adolescents that were qualitatively different from the adverse events seen in the other indications in children or adults with this treatment. J&JPRD has an extensive safety database of risperidone-treated children (1348 patients with DBD or autism), including 685 patients treated for more than 6 months of whom 332 were treated for over 12 months (data included in the Safety Update submitted with the complete response of 18 November 2004). Risperidone has been on the market since 1993 for the treatment of adults, and since 2001 for the treatment of children, in more than 25 countries worldwide. It should also be noted that risperidone is widely used in current off-label clinical practice in children in the US, and physicians are familiar with recognizing the adverse events associated with risperidone.

There is no evidence in the Company's Pharmacovigilance Database to indicate that the administration of risperidone to patients aged 5 to 17 years results in a safety profile that is qualitatively different to that seen in clinical trials or for all other age groups or populations. The most recent PSUR for risperidone adequately reflects the cumulative safety profile for the administration of risperidone to children in this age group and supports the current safety information in the label. The Company is prepared to propose educational guidance to physicians for specific adverse events of concern, and to review these plans with the Division.

The incidence of adverse events in children and adolescents with autism who received risperidone in the pivotal trials should be viewed in the following context:

a) In one of the pivotal studies, RIS-USA-150, many adverse events were elicited through a questionnaire, rather than via spontaneous reporting as is commonly performed in clinical trials. This may have led to an increased reporting of adverse events.
b) Children with autism commonly have fidgetiness, movements, and posturing that are inherent to this medical condition. These symptoms can often be incorrectly reported as adverse reactions to medication or can even mimic extrapyramidal symptoms (EPS). There was no systematic screening for movement disorders inherent to autism through parental interviews at baseline. ESRS, AIMS and physical examination at baseline are cross-sectional clinical assessments. These cannot substitute for a history from a parent, as some movement problems are not continuously present, may come and go within days, and may not be present during an ESRS or other rating. Follow-up data from investigators on all of the dyskinesia cases that were reported as "not recovered' (see Appendix 15 of the supporting document) have confirmed that there were a variety of involuntary movements at baseline, and or that the involuntary movements reported as "dyskinesia' were either intermittent manifestations of the underlying autistic disorder, or early onset transient movement disorders with resolution of symptoms.
c) The vast majority of children and adolescents with autism who experienced somnolence or other adverse events were treatment-naïve. This is in contrast with patients, especially adults, being treated for other psychiatric disorders, who have often experienced and adapted to adverse events of psychotropic medications before participating in a formal study. Antipsychotic treatment naïve patients are known to be more sensitive to the adverse events of these drugs.

In our complete response of 18 November 2004, we summarized adverse events by mode dose group (≤1 mg, >1 to <2 mg, and ≥2 mg). For many adverse events, most notably somnolence, confusion, and Parkinsonism, there was a higher incidence of adverse events in the lower mode dose groups. Conversely, for other adverse events such as fatigue, there was a suggestion of increasing incidence with higher mode dose group. The finding of adverse events at lower doses may reflect a combination of the majority of patients being medication-naïve and the trial using a flexible dose titration design, where investigators likely adjusted dose on the basis of efficacy as well as tolerability findings.

Coding of Adverse Events

In the 19 May 2005 letter, the FDA reiterated their concern that cases coded to "nervousness" or "agitation" may have been events of "akathisia". In response to this comment, we have recalculated the rate of EPS-related adverse events (see Section 6.1.4 of the supporting document), with agitation, nervousness and anxiety all being included as EPS-related adverse events. This reanalysis showed a reduction in the difference between risperidone and placebo with respect to EPS-related adverse

events, from 27.6% vs. 10.0% (original analysis) to 40.8% vs. 26.3% (re-analysis), respectively. The smaller difference between risperidone and placebo after re-analysis reflects a higher number of subjects with nervousness or agitation after receiving placebo compared with risperidone-treated subjects.

The FDA also raised a concern that some events coded to "dyskinesia" may have been tardive dyskinesia. In response, we have re-examined patient narratives in detail and have obtained further clinical follow-up information from the investigators (see Appendix 15 of the supporting document). Five patients had reports of dyskinesia, 2 of whom had a reported outcome of recovery during the clinical study suggesting that this was not tardive dyskinesia. In all 3 remaining patients, new follow-up information confirmed that the movements were either present at baseline, before administration of risperidone, and/or the events had an early onset, were intermittent during treatment, and eventually resolved; the investigators concluded that in all of these cases the movements were very unlikely to be tardive dyskinesia. Based on the clinical course, time of onset of dyskinesia symptoms relative to starting risperidone treatment, and the eventual resolution of symptoms, these events cannot be categorized as tardive dyskinesia. As mentioned previously, patients with autism have a variety of mild to severe movements, posturing and stereotypies that can be incorrectly assessed by a rater as dyskinesia associated with medication treatment. Taken together, these data support the Company's position that reports of dyskinesia in the clinical trials are not likely to be miscoded events of tardive dyskinesia and that the incidence of tardive dyskinesia is not a safety concern.

Long-Term Safety

With regards to the FDA's concerns on long-term safety, we have reviewed the events of dystonia and dyskinesia, as well as prolactin, growth and maturation. This should be viewed in the context of information provided in the complete response (18 November 2004).

In reviewing all cases of dystonia and dyskinesia as described above, we have confirmed that these events resolved during the course of the pivotal trials or during follow-up, and did not meet the criteria for tardive dystonia or tardive dyskinesia.

As reported in the most recent Safety Update (18 November 2004), a detailed review of prolactin in children with DBD treated for up to 12 months showed that, while mean prolactin levels increased in the first few weeks of treatment, mean levels peaked at approximately Weeks 4 to 6 and returned to within normal limits by Month 12. A review of the safety information did not show a correlation between prolactin levels and adverse events that are potentially attributable to prolactin. Further, in a separate analysis in children and adolescents with DBD who were treated with risperidone for up to 12 months (Dunbar et. al., Amer. Jour. Psychiat, 2003), there was no delay in growth and maturation observed in children and adolescents treated with risperidone.

Efficacy and Proposed Dosing Regimen

Data provided in this sNDA included findings from two trials, RIS-USA-150 and RIS-CAN-23, which were designed and conducted independently of each other. Study RIS-USA-150 Part 1 (National Institute of Mental Health [NIMH]-sponsored study), was designed by experts in autism at the Research Units on Pediatric Psychopharmacology (RUPP) group, a consortium of academic investigators. The concept and impetus for study RIS-CAN-23 (the J&JPRD-sponsored study) came from experts in autism at Dalhousie University and the University of Toronto, Canada. These trials were not designed as pivotal trials to support an sNDA submission. However, on examining the results, experts and key opinion leaders in the fields of autism and child psychiatry strongly advocated that the data from these trials provided significant information relevant to the appropriate treatment of autism, and recommended that the Company seek a marketing authorization for this indication based on the results of these trials. With the approval of this application, the Company seeks to market this important therapeutic option for children and adolescents with autism as quickly as possible, with appropriate guidance to physicians included in the RISPERDAL label.

Risperidone clearly demonstrated consistent efficacy in children and adolescents with autism, as short-term treatment and for relapse prevention. All of the effect sizes on the primary and secondary endpoints comparing risperidone to placebo in the pivotal clinical trials were moderate to large in favor of risperidone. Risperidone was not only effective in a wide range of behavioral symptoms, but also on stereotypies and other manifestations of autism. Therefore, we believe that the data from these trials adequately support the efficacy of risperidone in the treatment of irritability associated with autism.

The Company's proposed dosing recommendations for children and adolescents with autism are to initiate treatment at a dose of 0.25 mg/day or 0.5 mg/day and target a recommended dose of 0.5 mg/day or 1 mg/day, in patients weighing <20 kg or ≥20 kg respectively. The Company also recommends a slower and more cautious approach to dose increases, if clinically required, with the possibility of taking divided daily doses or reducing the daily dose where appropriate. This principle of "start low, go slow" allows the optimal balancing of efficacy with safety and tolerability, based on data from the pivotal trials. It is proposed that any dose increases should only be considered after a sufficiently long observation period (about 2 weeks) and should occur in small increments only (0.25 mg or 0.5 mg, respectively). This approach will ensure adequate exposure to a lower dose, allow assessment of efficacy and tolerability on a frequent basis, and establish a low, effective and well-tolerated dose on a patient-by-patient basis in clinical practice. This strategy is in line with the treatment of this population, where there is considerable variation in efficacy and tolerability responses between children, and will have to be utilized even if additional dose-finding data are obtained, given the heterogenous nature of the population.

Since the pivotal trials of risperidone in children and adolescents with autism were based on a flexible dosing design, they precluded identification of a minimum effective dose. However, it is evident from the data that, at doses ≤1 mg, some

children showed a trend towards a clinically relevant response at Week 1 and a pronounced clinically relevant response over placebo at Week 2. A sub-group of children benefit from judicious dose increases, but the maximum dose studied did not exceed 1.5 mg/day in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, or 3.5 mg in patients weighing over 45 kg, and there were few patients in the autism safety database who had a dose above 3 mg.

The proposed dosing recommendations for the treatment of children and adolescents with autism provides relevant information for the appropriate use of risperidone in these patients, and is actually more conservative than that which is typically used today in clinical practice. To better understand how risperidone is currently prescribed in children and adolescents with autism in off-label clinical practice, the Company analyzed data on the use of risperidone collected from prescription claims databases. These data show that risperidone is commonly prescribed at median doses of 1.25 mg/day in children aged 6 to 12 years and 2 mg/day in 13 to 17 year olds. Moreover, 54% of 6 to 12-year-olds and 62% of 13 to 17-year-olds received more than 1 mg/day risperidone, and 13% and 20% of the respective age groups received more than 3 mg/day risperidone. Therefore, in off-label clinical practice, doses have been and currently are being used in children and adolescents with autism that are substantially higher than the recommended doses currently being proposed (0.5 mg for patients <20 kg; and 1 mg for patients >20 kg).

Although we are confident that our proposed dosing recommendations are appropriate and clinically compelling, the Company is prepared to conduct a multiple fixed-dose Phase 4 trial to explore a minimally effective dose. These data would be utilized to further refine the risperidone dosing recommendations for this indication if necessary. It should be noted, however, that individual patients respond to and tolerate a range of doses in clinical practice. Furthermore, adverse events have been noted even at the lowest doses studied (≤1 mg), so one can also reasonably expect to see adverse events in this population at even lower doses studied in the future. Treating physicians will, therefore, have to assess the benefit versus risk of treatment with risperidone in the context of the seriousness of, and the level of disability caused by, the symptoms of autism in a particular child or adolescent.

Conclusion

It remains the Company's position that the pivotal trials, RIS-USA-150 and RIS-CAN-23, provide substantial evidence for a positive benefit-risk ratio for risperidone in the treatment of irritability associated with autism in children and adolescents. We consider risperidone to be an important therapeutic option for the treatment of irritability associated with autism, a serious medical disorder for which no approved drug treatment is available.

In the Company's opinion, the Agency's concerns stated in the Non Approvable Letter have been completely addressed, as summarized below:

a) Adverse events in children and adolescents with autism were typically mild to moderate, transient, and rarely lead to discontinuation. Overall, the tolerability profile seen with risperidone use in autistic children and adolescents was qualitatively similar to that in children or adults suffering from other psychiatric disorders and treated with risperidone.
b) On review of adverse events, the Company confirmed that coding of events of akathisia and dyskinesia was accurate.
c) There were no long-term safety or tolerability concerns with risperidone treatment in children and adolescents based on a comprehensive review of the J&JPRD safety database for risperidone. Specific review of cases of dystonia and dyskinesia confirmed that these cases did not likely meet the criteria for tardive dystonia or tardive dyskinesia. The increases in prolactin levels noted on initiation of risperidone treatment normalized after 12 months of treatment, with no long-term adverse effects. There was also no delay in growth and maturation in children and adolescents treated with risperidone for up to 12 months.
d) The proposed dosing recommendations for RISPERDAL, based on the principle of "start low, go slow", are appropriately cautious and will allow prescribers to reliably identify a low, effective and tolerable dose on a patient-by-patient basis. This information in the RISPERDAL label will provide important information for prescribers to support the most appropriate use of this product in the treatment of autism.

Considering these points, J&JPRD strongly disagrees with the conclusions in the FDA Not Approvable Letter. From 9 February 2005 to 2 May 2005, the Company proactively and repeatedly sought to actively engage the Division in discussions, to ensure that any concerns on these data could be addressed and to avoid delaying potential approval of this important medication for pediatric patients with autism. We regret that we did not have the opportunity to have such a discussion before the 19 May 2005 action date.

With this correspondence, the Company requests a meeting with the Division and Dr. Temple to further discuss the issues raised in the Not Approvable Letter and seek to resolve these with the Agency. Approval of this indication will not only bring evidence-based medical practice to children and adolescents suffering from autism, but will also provide appropriate safety and dosing guidance to physicians for the use of risperidone in this population. It is J&JPRD's position that it is important to have an opportunity to work with the Agency to reach agreement on this application. We look forward to your consideration that we have addressed all of the Agency's concerns, and can support approval for the use of risperidone in the treatment of irritability associated with autism, and our request to meet to resolve these issues together with the Agency.

This electronic submission is contained on one CD ROM. J&JPRD certifies that we have taken precautions to ensure that the CD ROM is free of computer viruses and authorizes CDER to use antivirus software, as appropriate. The following software was run to check for viruses: McAfee Virus Scan, v.7.1.0, scan engine 4.4.00, copyright 1993-2003, Network Associates Technology, Inc. The size of the submission is less than one megabyte.

If you have any questions regarding this submission or require additional information, please do not hesitate to contact me at (609) 730-6212.

Sincerely,

Johnson & Johnson
Pharmaceutical Research & Development, L.L.C.

Harindra R Abeysinghe, PhD
Associate Director
Regulatory Affairs

cc; Robert Temple, MD, Acting Director for ODE I

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	16 AUG 2005
TELEPHONE NO. *(Include Area Code)*	*FACSIMILE (FAX) Number (Include Area Code)*
609-730-6212	609-730-3091
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*) NDA 20-272/S-036

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
risperidone	RISPERDAL® Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one		R064766
DOSAGE FORM: Tablets	STRENGTHS: 0.25, 0.5, 1, 2, 3, 4 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of irritability associated with autism

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION
Response To FDA Action Letter For Autism & Request For Meeting

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 20-588/S-024, NDA 21-444/S-008

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* **Response To FDA Action Letter For Autism & Request For Meeting**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Harindra Abeysinghe	**Harindra R. Abeysinghe, Ph.D.** **Associate Director, Regulatory Affairs**	16 AUG 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200	**(609) 730-6212**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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Department of Health and Human Services
Food and Drug Administration
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1401 Rockville Pike
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From: Pandina, Gahan [JANUS]
Sent: Wednesday, February 20, 2002 1:50 PM
To: Reyes-Harde, Magali [JANUS]
Cc: Gharabawi, Georges [JANUS]; Mahmoud, Ramy [JANUS]
Subject: RE: AACAP prolactin abstract

Hi Magali! I have three comments specifically on the abstract, one editorial and two that are quite important. Although I thought that these had been caught (I was forwarded the abstract at one point last week), it appears not, and we will need to track them in the future.

Here is the abstract:

Objective: To explore the effect of long term risperidone use on prolactin levels in children.
Methods: Five clinical trial databases (double blind and open label) were merged and an exploratory analysis was conducted at different timepoints: 592 children with 7 weeks risperidone treatment, 550 with 3 months treatment; 499 with 6 months treatment and 400 with * 12 months. The primary analysis population (PAP) consisted of children with pre-dose and at least one post-dose prolactin observation at or after week 4.

(PAP) can be removed, as it is not mentioned elsewhere in the abstract, and just takes up space.

Results: Prolactin levels at baseline (pre dose trial medication) were a mean of 7.4 ng/ml, rose to a mean of 29.7ng/ml during weeks 4-7 and thereafter levels decreased and within 12 months had returned to within normal limits (mean 15.6 ng/ml) for the majority of children. Less than 6 % of children had prolactin related side effects. There appeared to be no correlation between prolactin levels and prolactin-related side effects.

I thought that our entire point of the prolactin ad board was that prolactin levels less than 30 were normal, and of no clinical significance. If we refer to a normalization as opposed to a return to baseline, doesn't this assume that the levels were abnormal in response to the rise in treatment? We need to think in the future about how we would like to phrase this change, as this connotes a problem that remits, as opposed to an insignificant rise in a peripheral lab value that completely diappears with time. We also refer to the majority of children, which implies that in some prolactin does not decrease, and then would continue to be "abnormal".

We also mention that there "appeared to be no correlation between prolactin levels and prolactin-related side effects". As these are called prolactin-related side effects, how would they not be related?!? We will need to come up with a different convention, such as symptoms associated with high prolactin levels e.g., above XXX. Otherwise, it says that despite finding these symptoms we are just disregarding their co-occurrence.

I think more work will need to be done prior to presentation at AACAP, and perhaps we can sit with Vivek and the endocrinologists to discuss further.

Conclusion: Despite transient increases in prolactin levels after 4 weeks of risperidone therapy, mean prolactin levels returned to within normal limits with 12 months with no serious sequelae.

Lets discuss further as we get closer. Also, was Dr. Kusumaker part of the advisory board? I realize that he has recently joined Janssen, but did not realize he attended this meeting and was involved in the analysis process.

Gahan

-----Original Message-----
From: Reyes-Harde, Magali [JANUS]
Sent: Tuesday, February 19, 2002 7:29 PM
To: Pandina, Gahan [JANUS]
Subject: FW: AACAP prolactin abstract
Importance: High

FYI

-----Original Message-----
From: Julian Ball [SMTP:julianball@wellshealthcare.com]
Sent: Wednesday, February 13, 2002 5:26 AM
To: 'Binder, Carin [JOI]'; robert.findling@uhhs.com; vivek.kusumakar@dal.ca; Dunbar, Fiona [JOI]; Derivan, Albert [PRDUS]; De Smedt, Goedele [PRDBE]; mschulz@scian.com; aleung@scian.com; Theeuwes, Margaret [JJCUS]; Nys, Vincent [JanBe]; Reyes-Harde, Magali [JANUS]
Cc: Riccardelli, Rosanna [JOI]; Pandina, Gahan [JANUS]
Subject: RE: AACAP prolactin abstract
Importance: High

Dear All

Please find attached prolactin abstract with educational objectives and key words.

Product:

Risperidone

Author:

Robert Findling

Title:

Prolactin Levels in Children after Long-Term Treatment with Risperidone

Target journal/conference:

AACAP/CINP

Key messages:

Children and adolescents who require treatment, along with their parents, can be confident in the data supporting the safety/tolerability of Risperdal in this age group.

Study number:

Draft number:

1

Agency writer:

Gill Sperrin/Julian Ball

Target submission date:

20 February 2002

Please return your comments to <name> by: <mm/dd/yy>

18 February 2002

Reviewer name <name> and signature