JANSSEN · PHARMACEUTICA · · RESEARCH FOUNDATION ·

RECORD OF FDA CONTACT

PRODUCT IDENTIFICATION: RISPERDAL® (risperidone) tablets and oral solution		
ORIGINATOR/SIGNATURE: [redacted]	DATE: 03 March 2000	
NDA NUMBER: IND NUMBER: 31,931	INITIATED BY: JANSSEN X FDA	BY TELEPHONE IN PERSON X
FDA PERSONNEL: See below	DIVISION: Neuropharmacological Drug Products TELEPHONE: (301) 594-5533	
SUBJECT: Minutes of March 3rd Meeting to Discuss RISPERDAL Pediatric Exclusivity and Development Program for Conduct Disorder		

Meeting Attendees:

FDA *Janssen Research Foundation (JRF)*

[redacted]

Summary: The objectives of this meeting were to discuss the requirements to obtain an additional six months market exclusivity as permitted under the FDA Modernization Act of 1997 and to discuss the clinical development plan for an indication in conduct disorder. The key issues discussed were:

Pediatric Exclusivity

- Pediatric exclusivity is not possible based on safety and PK alone (as proposed). Exclusivity must be based on the approved indication.
- FDA will issue a written request that contains a controlled trial in schizophrenia. JRF will submit a proposal for this controlled trial in adolescents (>13 years old); younger children will not need to be studied.
- The proposed PK trial was acceptable and if needed, JRF could enroll a mixed diagnosis (conduct disorder, schizophrenia) population.

Conduct Disorder (CD) as an Indication

- FDA questioned the validity of CD as a diagnosis and even the concept of CD as a disorder.
- They stated that even though CD is in DSM-IV that does not mean it is a disorder warranting an indication in the label.
- FDA feels a public hearing is needed to define how to look at CD. Their main concern is that RISPERDAL or any other product would be used as a chemical straight jacket. This is the reason the issue needs to be publicly debated.
- FDA believes aggression is synonymous with CD.
- We could proceed with the two trials proposed (RIS-USA-161, RIS-USA-222). However, even if these trials are positive, they would want a consensus advisory committee meeting to confirm the disorder exists. This advisory committee meeting would be triggered by the review of our supplemental application.
- The Division is willing to work with us to define scales for CD and would like to see our data to show their validity and reliability.

Details: A briefing package was submitted on February 10, 2000 (Serial No. 237) in which background information was provided to address questions proposed by Janssen. The questions were divided into two sections, pediatric exclusivity and registration strategy for conduct disorder, and served as the agenda for the meeting. Although we did not discuss each question individually, the issues raised in the questions were discussed in general. The questions and associated discussion points are provided below.

Pediatric Exclusivity

- *Is RIS-USA-160 adequately designed to provide sufficient pK/safety data for inclusion in the labeling for a pediatric population?*
- *Will a written request be issued based on the pharmacokinetic data from the proposed trial RIS-USA-160, as well as the safety data from trials RIS-USA-93, RIS-CAN-19, RIS-USA-97, RIS-CAN-20 and RIS-INT-41?*

[redacted] indicated that they want to see at least 1 controlled trial in the indication we already have approved in order to obtain pediatric exclusivity. They don't believe that submitting only PK and safety data is in the spirit of the pediatric exclusivity provision, unless we can prove schizophrenia is the same in pediatric and adults. So far they have not seen a credible argument that the two populations are the same and did not think it was a worth while endeavor for us to try to prove. Because the safety data proposed is not from a schizophrenic population, it can not be handled appropriately in the label since it would be considered an implied claim. The safety and PK data for pediatrics may be useful, but there are other ways to convey this information to physicians.

For the controlled trial, FDA thought the appropriate pediatric subgroup to study in schizophrenia would be adolescents 13 to 16 years old. Although there are some schizophrenic patients as young as 10 years old, they did not think it would be possible to enroll enough patients in this younger age group. FDA felt they had enough information to issue a written request, however, we suggested that we submit a proposal for the study for them to base the written request on. FDA agreed this would be helpful.

In regards to the proposed PK trial, FDA did not have any specific comments and believed it would provide useful information. They did not have any concerns that the age groups being proposed were younger (5-16 years old), as long as this information was being generated to support an indication in younger patients. FDA also indicated that it is acceptable to study a mixed diagnosis (conduct disorder, schizophrenia) population in the PK trial.

Registration Strategy for Conduct Spectrum Disorder

- *Does the Division support the use of the term "conduct spectrum disorder" to describe conduct disorder, oppositional defiant disorder and disruptive behavior disorder not otherwise specified, in children?*
- *As a follow-up to the letter from the Division on January 22, 1997, does the Division agree with our proposed clinical development plan to support the indication of Conduct Spectrum Disorder, including Conduct Disorder (312.8), Oppositional Defiant Disorder (313.81) and Disruptive Behavior Disorder Not Otherwise Specified (312.9), in children ages 5-16 without mental retardation?*
- *In studies RIS-USA-161 and RIS-USA-222, the Nisonger Child Behavior Rating Form - modified version (N-CBRF), will be used to assess efficacy. The Conduct Problem subscale of the N-CBRF will be the primary outcome variable of these trials. Secondary efficacy parameters will be based on the Conners Parent Rating Scale (CPRS) and Clinical Global Impression (CGI). Does the Division agree that these are the appropriate parameters for evaluating non-mentally retarded children with conduct spectrum disorder?*

- *Are the proposed studies RIS-USA-161 and RIS-USA-222 adequately designed to evaluate the safety and efficacy of risperidone in non-mentally retarded children with conduct spectrum disorder?*
- *Are the available data and data from the proposed trials adequate to support a new indication for risperidone for the treatment of conduct spectrum disorder in pediatric patients (ages 5-16) without mental retardation?*

FDA questioned the validity of conduct disorder (CD) as a diagnosis and even the concept of CD as a disorder. They don't believe it is well accepted outside the child psychiatrist community. FDA acknowledged CD as a valid clinical entity as it is included in DSM-IV, however elevation of a disorder to permanent status in DSM does not make it a disorder warranting an indication in the label.

FDA believes CD is synonymous with aggression and thinks we are trying to get approval of aggression under the guise of CD. Although we strongly disagreed, FDA indicated that they feel the problem is in the nature of the diagnosis because it is just a "list of behaviors", mainly aggressive behaviors that annoy others. If CD is just a form of aggressive behavior, they recommended that we study this from a symptom approach and look at aggression straight on. If the symptom approach were taken, FDA would expect us to look at the effects of RISPERDAL in three models. The suggested populations to examine were dementia, mental retardation, and conduct disorder. However, the first step in looking at aggression would be to get agreement publicly (e.g., an advisory committee meeting) on how to define aggression and the best way to measure it. FDA acknowledged it would take time to get public agreement and that this approach may not be the easiest way to get approval.

FDA commented that they do not often question a diagnosis, but in the case of CD they are. They feel a public hearing is needed to define how to look at CD and if it is an indication that society is willing to treat. Their main concern is that RISPERDAL or any other product would be used as a chemical straight jacket. Although CD has been discussed publicly at several conferences, the conference audiences have been only child psychiatrists. FDA would require this type of issue to be discussed by a wider scope of psychiatrists, so that the entire psychiatric community can weigh in on the decision, similar to discussions regarding behavioral disturbances in dementia at the March 9, 2000 Psychopharmacological Drug Advisory Committee meeting.

In the absence of a public hearing, either on aggression or CD itself, FDA could not assure us that we would be able to get an indication in the label, even with two positive trials. They emphasized again that they are uncertain whether CD is a diagnosis that merits treatment.

In regards to the two trials proposed (RIS-USA-161, RIS-USA-222), the FDA commented that they have no experience with the scale selected (Nisonger Behavior Rating Form). Based on the information we provided, (Attachment 1), they did not feel the subscale of the Nisonger mapped well to CD, and it was more of a combination of Oppositional Defiant Disorder and CD. This is based on the questions "talks back to teacher, parents, or other adults," "stubborn, has to do things own way," and "disobedient". We commented that we have experience with the Nisonger scale and believe it has a better CD subscale than the Conners rating scale does.

FDA asked about the validity and reliability of the Nisonger scale. We provided an article by Aman, et al (Attachment 2) to demonstrate validation in a mental retardation (MR) population. FDA indicated that they would not extrapolate from the MR population to the non-MR, and that we would have to validate the use of the scale in the non-MR population as well. We informed them we are in the process of doing the validation in the non-MR population. To address reliability, we offered to send the available clinical data we have generated along with any literature references. FDA requested that the clinical data provided include an item analysis.

Until FDA reviews the validation and reliability data, they can not accept the use of the Nisonger scale as the primary endpoint. We asked if they preferred us to use another scale (i.e., Conners), but they

indicated they did not have an alternative scale for us to use. The subscales of the Conners rating scale was provided to FDA for their review as well (Attachment 3).

We talked briefly about the length of the proposed trials. Although 6 weeks is short, they thought it is an acceptable duration for the trials. In chronic conditions, they would like to see that the drug effect persists, and that may not be accomplished in a 6 week trial. If we decide to do 6 week trials, they requested that we provide a rationale as to why trials of longer duration are not possible (e.g., because of a high drop out rate).

With regards to safety, we pointed out that our long-term data in pediatrics would be in a MR population. FDA did not think this would taint the non-MR safety data, but we would need to address how the MR data is relevant in any application. The number of pediatric patients with long-term exposure to RISPERDAL (>300) is not robust, but is generally the exposure numbers the Division is used to seeing. FDA commented on the high rate of somnolence (50%) presented in the background package for RIS-USA-93 and pointed out that this will be a problem if it is a chronic effect. We explained that additional analyses of the data have been performed which showed that this effect was not tied into efficacy.

It was emphasized in conclusion, that if we choose to proceed with the two proposed trials, even if they are positive, FDA would want a consensus advisory committee meeting to confirm that CD is a disorder worthy of treatment and requires a separate indication in the label.

Action Item: Submit available clinical data on the reliability of Nisonger scale.

g:\wpdocs\cns\risperdal\filenotes.all\030300_minutes.doc