DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

NOV 25 2014

Stephen A. Sheller, Esq.
Christopher A. Gomez, Esq.
Sheller, P.C.
1528 Walnut Street, 4th Floor
Philadelphia, PA 19102

Re: Docket No. FDA-2012-P-0857

Dear Mr. Sheller and Mr. Gomez:

This responds to your citizen petition received on July 27, 2012, and amended on August 27, 2012.[1] Your petition, as amended,[2] requests that the Food and Drug Administration (FDA or Agency) revoke the pediatric indication for Risperdal (risperidone), for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated. Alternatively, you request that FDA require a new boxed warning for Risperdal and all generic versions of risperidone that would warn of what you characterize as a lack of sufficient safety data. Finally, you also ask that FDA direct Johnson & Johnson, Inc. (J&J) to consent to release you from any and all standing Confidentiality/Protective Orders so that you can present to the Agency "internal documents and data, as well as an expert analysis thereof," which you believe support your requests (Petition at 2).

We have carefully considered your petition and the comments submitted to the docket. For the reasons described below, your requests are granted in part and denied in part.

I. BACKGROUND

A. Risperdal and Invega

Risperidone and its active metabolite, paliperidone, are antipsychotic drugs marketed in

[1] We also acknowledge your March 26, 2013, letter to FDA requesting that the Commissioner of Food and Drugs schedule a hearing to discuss your petition. In addition, we acknowledge your July 2, 2013, letter reiterating certain requests contained in your petition. We responded to these letters and posted both the letters and our responses to the docket associated with your petition.

[2] Your August 27, 2012, submission, which you characterize as an "amendment" to your August 2, 2012, petition, appears to be a replacement of your original petition. It contains some additional discussion in support of your requests but is otherwise identical to the original. Accordingly, we refer to your August 27, 2012, submission as the "Petition" or "your petition" throughout this response, and do not further refer to your original August 2, 2012, submission.

the United States as Risperdal and Invega, respectively. Risperdal (risperidone) is the subject of new drug application NDA 20-272 and was approved on December 29, 1993. It was indicated for the management of the manifestations of psychotic disorders. An additional indication for treatment of irritability associated with autistic disorder in children and adolescents was added in 2006. In 2007, the indications for schizophrenia and bipolar I disorder were expanded to include adolescents aged 13-17 and children and adolescents aged 10-17, respectively.

Invega (paliperidone) Extended-Release Tablets was approved on December 19, 2006. It is the subject of NDA 21-999. It was indicated for the treatment of schizophrenia. It is designed to deliver paliperidone — the active ingredient derived from risperidone.

Both drugs are known to elevate blood levels of prolactin, a naturally occurring hormone produced by the pituitary gland in the brain. Elevated levels of prolactin (hyperprolactinemia) from any cause can be associated with a number of clinical effects, including breast enlargement (also called gynecomastia).

Both Risperdal and Invega have been studied in adequate and well-controlled clinical trials in pediatric patients. As noted above, supplemental new drug applications (sNDAs) for the use of Risperdal in the treatment of irritability associated with autistic disorder in children and adolescents (ages 5-16 years), treatment of schizophrenia in adolescents (ages 13-17 years), and treatment of bipolar disorder in children and adolescents (ages 10-17 years) were approved on October 6, 2006; August 22, 2007; and August 22, 2007, respectively. An sNDA for the use of Invega in the treatment of schizophrenia in adolescents (ages 12-17 years) was approved on April 6, 2011.

B. Regulatory Framework

FDA's regulation of drug safety is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et. seq.) and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations). The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved NDA or abbreviated new drug application (ANDA).[3] Before approving an NDA, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[4]

After an approved drug enters the marketplace, FDA may have cause to reassess its safety and take regulatory action if warranted and appropriate. One possible action is withdrawal of a drug product's approval. Section 505(e)(1)-(2) of the FD&C Act provides that FDA shall withdraw approval of a drug product if the agency finds, after notice and opportunity for a hearing, that "clinical or other experience, tests, or other

[3] See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).

[4] Section 505(b)(1) of the FD&C Act; section 505(d) of the FD&C Act.

scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved," or that:

> . . . new evidence of clinical experience, not contained in [the] application or not available to the Secretary until after [the] application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when [the] application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.

Another possible regulatory action would be to require the inclusion of new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, in product labeling (see section 505(o)(4) of the FD&C Act).

II. DISCUSSION

A. Request to Revoke Pediatric Indication or Require a Black Box Warning[5]

You request that the FDA revoke the pediatric indication for Risperdal (including all generic versions of risperidone) and Invega unless and until the long-term safety of these drug products can be demonstrated. Alternatively, you request that FDA require a boxed warning for Risperdal and all generic versions of risperidone (Petition at 1, 2).

You base your requests on the incidence of adverse events associated with Risperdal and Invega, including hyperprolactinemia and gynecomastia. You assert that the current labeling of these products fails to adequately inform and guide prescribers and contend that, as a result, patients who might otherwise be provided with alternative treatments are led to suffer adverse effects associated with Risperdal. As grounds for your request to revoke the pediatric indication or require a black box warning, you cite a lack of long-term safety data for these drug products.

For the reasons discussed below, we disagree with your assertion that what you characterize as a lack of long-term safety data is a basis for either revoking the pediatric indications for Risperdal or Invega or adding a new boxed warning to the labeling of these drug products.

1. Safety Information Supported Approval of Pediatric Indications; Subsequent Review Does Not Alter Our Conclusion

Before the approval of each pediatric indication for Risperdal and Invega, the Agency

[5] You note that your requests and the grounds for your requests apply to Risperdal (including generic versions of Risperdal) and Invega, though you do not specifically request a boxed warning for Invega (Petition at 1).

determined that sufficient short-term and long-term safety information to support approval had been presented by the drug sponsor.

Since the pediatric approvals were granted, we have: (1) examined required Annual Report submissions for any new safety signals related to Risperdal and Invega; (2) routinely monitored Agency data, including our adverse event reporting systems, for new safety signals; (3) asked for and received from the drug sponsor any data in their possession relevant to the use of Risperdal or Invega in children or adolescents that had not previously been submitted; and (4) conducted a thorough review of published literature[6] to identify any new safety concerns, including any concerns related to the long-term use of these drug products.

In sum, based on reviews of clinical data submitted by the sponsor, published literature, and postmarketing surveillance, there is no evidence that the drug is unsafe, and no evidence that the drug is not shown to be safe, for use under the conditions of use upon the basis of which the applications were approved that would warrant revocation of the pediatric indication of these drugs.

2. *The Absence of Additional Long-Term Safety Data Does Not Support Revoking the Pediatric Indications for Risperdal and Invega*

We acknowledge that we lack quality, long-term, comparative safety data on the use of antipsychotic agents in the pediatric population. Indeed, the lack of such data is a common theme emphasized throughout the relevant published literature.

Unfortunately, long-term, randomized, placebo-controlled drug safety trials are often not feasible, and that is the case here. Among other considerations, it is unethical to require acutely ill patients to be randomized to placebo and be observed for several months or more without effective treatment. Trials that use another active drug as the comparator instead of placebo might be conducted, but the results of such trials would be difficult to interpret because the absolute risk attributable to the other active drug may not be known or evaluable. Likewise, simply following patients receiving these drugs for a long time with no control group would produce data that would be highly challenging to interpret because it would be unknown whether any observed differences should be attributed to the drug, passage of time, or intercurrent factors. Finally, retention of patients in long-term studies can be difficult, and if a large number of patients drop out over the course of a study, its conclusions may be substantially weakened. For these reasons, assessment of the effects of long-term drug exposure primarily relies on animal data,[7] together with any

[6] Our literature search set out to identify any published adequate (placebo or active-controlled) trials in children or adolescents that provided data with respect to preselected adverse events associated with the use of the new generation antipsychotic drugs (i.e., risperidone, paliperidone, aripiprazole, olanzapine, and quetiapine). These drugs were selected because they have approved pediatric indications. Our search focused on long-term safety data referencing those adverse events we believed to be most important in the pediatric population: hyperprolactinemia, weight gain, hyperlipidemia, extrapyramidal symptoms, and tardive dyskinesia. The PubMed, Embase, and EBSCO Host were among the databases we used.

[7] In fact, before conducting studies in children, juvenile toxicity studies are conducted in young rats,

other relevant long-term safety information available to the Agency.

Thus, we acknowledge that not all adverse reactions associated with the long-term use of these drugs in pediatric patients are detected by clinical investigations or postmarketing surveillance. These include effects on measures such as growth and sexual maturation. We have no comparative data for known adverse events such as gynecomastia.

However, the lack of quality, long-term clinical safety information of the type discussed above is not an appropriate reason to revoke the pediatric indications of Risperdal and Invega when weighed against the potential therapeutic benefit derived from the use of these drugs.

Clinical efficacy of Risperdal and Invega in their approved pediatric indications was demonstrated prior to approval, and numerous pediatric patients have benefited from these drugs despite their known risks. Granting your request that the pediatric indications for Risperdal and Invega be withdrawn unless and until long-term safety is demonstrated would be tantamount to a long-term or permanent withdrawal, thereby removing an important and beneficial therapeutic option for many children and adolescents with these disorders. Withdrawal of these indications would constitute a disservice to the public health.

Accordingly, we do not believe that the standards for withdrawal of approval enumerated in section 505(e) have been met here. Based on reviews of clinical data submitted by the sponsor, published literature, and postmarketing surveillance, there is no evidence that the drug is unsafe, and no evidence that the drug is not shown to be safe, for use under the conditions of use upon the basis of which the applications were approved that would warrant revocation of the pediatric indication of these drugs.

3. There Is No Basis for Requiring a Boxed Warning Regarding Lack of Long-Term Safety Data Associated With Pediatric Use of Risperdal and Invega

FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" on a drug product's labeling (21 CFR 201.57(c)(1)).

As described in the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) (the Boxed Warnings Guidance),[8] a

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followed for a period corresponding to human childhood, to detect signals of potential adverse effects with long-term use in developing children. The following areas are assessed in these animal studies: (1) learning, memory, and general behavior (e.g., hyperactivity); (2) histopathology, which entails an examination of various body organs to detect drug-related injury, and (3) reproductive functioning upon reaching young adulthood (including evaluation of mating behavior, fertility, and offspring). See Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products (February 2006), pp.11-12.

[8] Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

boxed warning is ordinarily used to highlight for prescribers one of the following situations:

> There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug;
>
> *OR*
>
> There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation);
>
> *OR*
>
> FDA approved the drug with restrictions to ensure safe use because the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under [21 U.S.C. 355-1(f)(3)] "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).[9]

The Boxed Warnings Guidance also states that, infrequently, a boxed warning can be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it warrants inclusion in a boxed warning (Boxed Warnings Guidance at 11).

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate. For example, a contraindication for use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which an adverse reaction has not been observed. A boxed warning can also be considered for a drug that poses risk-benefit considerations that are unique among drugs in a drug class (Boxed Warnings Guidance at 12).

None of these situations is applicable here, and the concerns you have raised do not otherwise justify a boxed warning. The risks of treatment with these drug products, including the risks with which your petition is principally concerned, are well known.[10]

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[9] Boxed Warnings Guidance at 11.

[10] BJ Sadock, VA Sadock, and P Ruiz (eds.), Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 9th Edition (2009). Williams and Wilkins, pages 3215, 3217-3219.

Gynecomastia is a common clinical manifestation of hyperprolactinemia, regardless of cause,[11] and does not represent a serious adverse event as defined in 21 CFR 312.32(a). We would expect prescribers and patients to discuss these potential risks (together with the potential benefits) before and during treatment, consistent with the applicable standard of care.

Furthermore, we do not think it is appropriate to use a boxed warning to convey, as you request (Petition at 2), a mere *lack* of certain safety data (the long-term comparative safety data discussed in section II.A.2 of this response), particularly where, as we have previously discussed, the risks in question are already well known by prescribers and do not represent serious adverse events.

Finally, other antipsychotic drugs (such as haloperidol, fluphenazine, and perphenazine) have been known for decades to produce hyperprolactinemia as a side effect of their therapeutic action, and this fact is well known within the psychiatric community. The risk of hyperprolactinemia associated with certain antipsychotics has been basic textbook knowledge in psychiatry for many years. For example, there is considerable discussion of the tendency of antipsychotic drugs to elevate prolactin in *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, (4th edition, published by Cambridge University Press (2013)).[12] This is one of the standard textbooks in the field of psychiatric drug therapy.

Accordingly, your petition does not present any data, nor does the Agency possess any data, that would lead us to conclude that a boxed warning regarding the risk of gynecomastia or, more generally, hyperprolactinemia, is appropriate for the labeling of Risperdal or Invega. For these reasons, we deny your requests to require a boxed warning for Risperdal and all generic versions of risperidone.

B. Labeling Adequacy

Although your petition includes an extensive discussion of the current labeling of Risperdal and Invega, you do not make specific labeling requests other than the request, addressed above, that FDA require a new boxed warning for Risperdal and all generic versions of risperidone. We therefore do not respond to your specific contentions regarding the current labeling of these products. As is the case with all drugs regulated by the Agency, labeling is assessed as appropriate to ensure that it reflects all relevant safety information and labeling updates are sought and implemented as necessary.

[11] Id. at page 3218.

[12] See Page 336.

C. The 2008 Advisory Committee Meeting

Your petition (Petition at 9-13) references the FDA Pediatric Advisory Committee Meeting that was held on November 18, 2008,[13] and asserts that several follow-up actions/recommendations have not been undertaken, including:

1. additional follow-up regarding on-label and off-label product use of this class of drug products, with specific attention to age and indication for which the product is being used;

2. additional follow-up regarding metabolic syndrome, growth, sexual maturation, and hyperprolactinemia;

3. further studies on long-term effects in the pediatric population of this class of products;

4. additional follow-up on extrapyramidal side effects in the pediatric population; and

5. additional evaluation of this class of antipsychotic medications and concomitant drug use.

You do not explain how the 2008 Advisory Committee Meeting supports the specific requests made in your petition – in particular, that FDA revoke the pediatric indication for Risperdal, for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated; or, in the alternative, that FDA require a new boxed warning for Risperdal and all generic versions of risperidone that would warn of what you characterize as a lack of sufficient safety data. Moreover, we disagree with your contentions regarding asserted Agency inaction following the Advisory Committee meeting. The Agency has been actively engaged in the issues addressed at the 2008 Advisory Committee meeting and has followed up on the Advisory Committee's recommendations as appropriate and necessary.

D. Request for FDA to Direct J&J to Consent to Release Confidentiality/Protective Orders

You request that FDA direct J&J to release your firm from "any and all standing Confidentiality/Protective Orders" so that you can present to the FDA the "internal documents and data," as well as an expert analysis thereof, which you believe support your requested actions (Petition at 2). In the alternative, you ask that FDA request that J&J submit "all internal documents, including e-mails and correspondence, as well as documents and testimony from the Risperdal litigation" (Petition at 1, footnote 2). You further ask that should FDA make such a request to J&J, any documents produced by J&J

[13] Transcript available at http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4399m1.pdf.

should either be made available for public review and comment or made available to you for "in camera review" (Petition at 2, footnote 2). We refer collectively to these alternative requests as the "Additional Information Request."

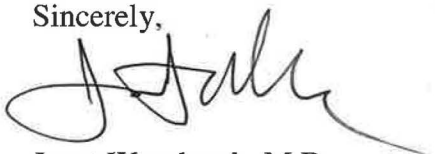
In response to the Additional Information Request, we asked J&J to provide any data in its possession relevant to the use of risperidone or paliperidone in children and adolescents that J&J had not previously provided to the Agency. We referenced your petition and your amended petition in our letter and included those documents as attachments to our letter. J&J provided certain information in response to our request, which we considered along with all other relevant information available to us in addressing your Petition. We decline to take any of the other specific actions you requested in connection with the Additional Information Request.[14]

Accordingly, the Additional Information Request is granted in part and denied in part.

III. CONCLUSION

For the reasons stated above, your requests are denied, except for the Additional Information Request, which is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[14] Given our disposition of the Additional Information Request, we need not reach, and make no comment on, our legal authority to take any of the specific actions you request in connection with the Additional Information Request.