Sheller P.C.
LAW OFFICES

1528 Walnut Street, 4th Floor * Philadelphia, PA 19102
215/790-7300 * www.sheller.com

2012 AUG -2 A 9:27

July 27, 2012

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg,

Sheller, P.C. represents individuals and groups of individuals who have suffered serious physical and mental injuries caused by prescription pharmaceuticals, biologicals and devices. We presently represent hundreds of individuals who have suffered serious harm, including gynecomastia and prolactin-related injuries as a result of their ingestion of the second-generation atypical anti-psychotic medications Risperdal® (risperidone) marketed by Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Janssen Pharmaceutical, Inc., a subsidiary of Johnson & Johnson (hereinafter "J&J").

Requested Action

We hereby petition the Food and Drug Administration (hereinafter "FDA"), pursuant to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§352, 321 and 21 C.F.R. §§10.30 and 7.45 **to immediately revoke the pediatric indication for Risperdal®, all generic version of risperidone, and Invega®[1] (an extended release and injectable medication which includes the same primary active metabolite as Risperdal®) unless and until the long-term safety of the drug can be demonstrated, or in the alternative to immediately require that labeling for Risperdal® and all generic versions of risperidone include a black box warning on the lack of sufficient safety data.** Additionally, the FDA should **direct J&J to consent to release Petitioner from any and all standing Confidentiality/ Protective Orders so that Petitioner[2] can**

[1] Given the pharmacologic similarity between Risperdal® and Invega®, the information set forth in the remainder of this Petition applies equally to both drugs. J&J's conduct with respect to Risperdal® demands that the FDA take the same remedial actions with respect to Invega® in order to protect the public.

[2] In the alternative, the FDA should request that J&J themselves submit all internal documents, including e-mails and correspondence, as well as documents and testimony from the Risperdal® litigation. However, given J&J previous submission of data to the FDA, in a manner likely to bury or gloss over significant adverse event information, it is imperative that any documents produced directly by J&J either be available

FDA-2012-P-0857

2012-6537 CP

present to the FDA the internal documents and data, as well as an expert analysis thereof which we believe support the foregoing requested actions.

Basis for Action

Interest of the Parties

Petitioner represents hundreds of children who have suffered Risperdal®-induced gynecomastia and prolactin-related adverse events as a result of their ingestion of Risperdal®. Our clients constitute a sample of the tens (if not hundreds) of thousands of children who have been prescribed Risperdal® (both on- and off-label) and who are at risk of suffering adverse events if the FDA does not take immediate action.

Nature of the Problem

Our own investigation has revealed that the long-term safety of Risperdal® for children has not been established, and that the current Prescribing Information does not adequately reflect the true risks posed by Risperdal®.

Specifically, and as explained in more detail below:

* The approved Indications for the use of Risperdal® in the pediatric population are unduly vague and lack appropriate guidance of physicians considering the use of the drug.

    * For example, while Risperdal® is approved for use in children diagnosed with Bipolar I, that condition is never defined or described, leaving the potential for the conflation of that condition with the more common Bipolar II Disorder and therefore the inadvertent expansion of off-label use of Risperdal®.

    * The approval for "irritability" associated with autism is so vague and ambiguous as to practically equate with an approval for treatment of Autism generally, which is something the FDA specifically has refused to do.

    * J&J's conduct prior to pediatric approval by the FDA has created a robust off-label market for Rispderdal for conditions far afield from the limited Pediatric Indication eventually approved by the FDA.

* At the same time, children are particularly susceptible to the significant increases in prolactin-levels which Risperdal® is known to cause. This fact, and its significance, is not adequately conveyed to physicians and patients in the Prescribing Information:

---

for public review and comment and/or made available to Petitioner for *in camera* review in order to assure the accuracy and completeness of J&J's document submission.

* The introduction of Risperdal® to pre-pubertal or pubertal adolescents enhances the hormonal and endocrinological processes already at work, resulting in substantially worse and more permanent conditions such as gynecomastia and adverse effects on sexual maturation than would have been experienced in the absence of Risperdal®. This fact is not warned about at all;

* The propensity of Risperdal® to cause weight gain is understated, leading physicians to inaccurately attribute any abnormal breast growth to weight-gain itself, and therefore fail to consider Risperdal® as a potential cause.

* Meanwhile, the Prescribing Information lacks clear guidance to physicians in terms of monitoring their pediatric patients' blood prolactin levels and obtaining complete physical exams, by qualified practitioners, to identify and assess abnormal breast growth or effects of hyperprolactinemia.

As such, our investigation validates the concerns raised by the FDA's own Advisory Committee regarding the safety of Risperdal® as labeled. As discussed in detail below, the Advisory Committee in 2008 found that the current Prescribing Information for Risperdal® was inadequate and issued a series of recommendations aimed at correcting the situation. To date, however, the Prescribing Information for Risperdal® remains unchanged and we have seen no evidence that J&J has provided the FDA with the information which the Advisory Committee found essential to the creation of an adequate prescribing label.

Background

Risperdal® was approved for adults by the FDA in 1993 as an anti-psychotic therapy for schizophrenia. In 2003 this adult indication was expanded to include use of Risperdal® for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults.

In 2006 Risperdal® received its first approval for children, for treatment of the irritability associated with autistic disorder in children between the ages of 5 and 16. In 2007 the adult indications for schizophrenia and bipolar I disorder were expanded to include adolescents as young as 13 and 10, respectively.

The manufacturer of Risperdal® has augmented these FDA-approved indications through aggressive "off-label" marketing, including the marketing of Risperdal® to children prior to the FDA's approval for use of the drug in that population.

Even after Risperdal® was approved for children in very limited circumstances, J&J has aggressively marketed the drug for off-label conditions such as Autism generally (even absent "irritability"), Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), Oppositional-Defiant Disorder (ODD), Conduct

Disorder (CD), Disruptive Behavior Disorder (BDB), Tourette's Syndrome, Post-Traumatic Stress Disorder (PTSD)[3] and Pervasive Developmental Disorder (PDD).

In so doing, J&J largely helped to fuel a veritable explosion of the anti-psychotic pharmaceutical sector. In 2011, sales of anti-psychotic medications in general totaled $18.2 billion, a 12.7% increase over 2010. Atypical anti-psychotics became one of the fastest growing medication classes in the nation.[4]

Risperdal® and Gynecomastia and Prolactin-Related Adverse Events

The current Prescribing Information for Risperdal® **fails** to even mention gynecomastia or hyperprolactinemia in the HIGHLIGHTS OF PRESCRIBING INFORMATION under either the "WARNINGS AND PRECAUTIONS" , "ADVERSE REACTIONS" or "USE IN SPECIFIC POPULATIONS" sections.

In fact, one must search 17 pages into the Prescribing Information to locate data about the rates of gynecomastia in child and adolescent trials. The label reads in relevant part:

> In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.[5]

This statement is misleading in that studies have demonstrated that the rate of gynecomastia is actually 5% with long-term use of RISPERDAL®, which clinical experiences shows is the most typical use of the drug.

Further, the statement, combined with the fact that data on the adolescent rates of Risperdal®-induced hyperprolactinemia and its associated disorders of: galactorrhea, amennorhea, infertility in girls; galactorrhea, gynecomastia and diminished libido in boys; and adverse impact on sexual maturation in children of both genders, are buried in the "USE IN SPECIAL POPULATIONS" section of the Prescribing Information, have given physicians and the public a false sense of the safety of Risperdal® for adolescents and concealed the epidemic of prolactin-related adverse events being inflicted upon children by Risperdal®

---

[3] Notably, after a study of risperidone for the treatment of PTSD conducted at Veterans' Administration Medical Centers, the United States Army recently gave Risperidone a "D-level Recommendation", meaning that the "harm outweighs benefit"). See: *Memorandum for Commanders, MEDCOM Regional Medical Commnds dated 4/10/12* at p.9. While this Army study involved adults, it demonstrates that the risk/benefit analysis that supported initial FDA approval of risperidone does not support the myriad off-label uses for which J&J has promoted the drug.

[4] . *See: (http://www.imshealth.com/ims/ Global/ Content /Insights/IMS%20Institute %20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf)*

[5] A copy of the Prescribing Information for Risperdal is attached as Exhibit A.

The role of Risperdal® in triggering the development of gynecomastia in young boys is particularly invidious, as Risperdal® is responsible for multiple adverse events that, individually or in combination, contribute to the development of abnormal breast growth in that patient population. Specifically, Risperdal® causes hyperprolactinemia particularly aggressively in adolescents, a population particularly susceptible to the adverse sequella of that condition, including gynecomatia and impaired sexual mauration. At the same time, Risperdal® can trigger substantial weight gain which itself increases the risk of the gynecomastia. These two Risperdal®-induced mechanisms combine to wreak havoc on an adolescent's endocrine system. The Risperdal®-induced weight gain is particularly serious because the propensity of Risperdal® to cause weight gain is understated in the Prescribing Information, which leads many prescribing physicians to incorrectly attribute the development of gynecomastia to either "over-nutrition" or puberty.

Indeed, the prescription of Risperdal® to children prior to or during puberty is particularly harmful given that the drug can both exacerbate pubertal gynecomastia and turn pubertal gynecomastia (which is typically a short-lived phenomenon) into a chronic condition often requiring surgical repair.

Nevertheless, the Prescribing Information for Risperdal® is silent on these risks, leaving physicians in the position of throwing gasoline on the hormonal and endocrine fire already simmering in their pre-puberty and puberty aged patients.

By contrast, when the anti-depressant EFFEXOR was found to have an increased risk of adverse events in pediatric patients, the following black-box warning was added to the Prescribing Information, **even though EFFEXOR is not even approved by the FDA for use in children**:

Rx only
Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk,

PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

Likewise, the website for EFFEXOR includes this black-box warning displayed prominently in two different locations on the medication's homepage.[6]

Compared to the responsible and prudent way in which a special pediatric risk is conveyed for EFFEXOR, the risk of hyperprolactinemia with Risperdal® is hidden like a needle in a haystack.

It is Petitioner's experience that misinformation such as exists in the Risperdal® prescribing materials results in the failure of physicians and patients to recognize, report and attempt to remedy adverse events such as Risperdal®-induced gynecomastia and prolactin-related conditions.

For example, RISPERDAL® and other anti-psychotic medications are often prescribed by mental health professionals who are not in the habit of conducting physical examinations of their patients, including assessments of adolescent/teen boys and young men for abnormal breast growth, Tanner staging, evaluation of testicular development and sexual maturation generally.. Young patients who are prescribed RISPERDAL® and risperidone (and their parents) are not instructed to be on the look-out for abnormal breast growth. The adolescent patients themselves who are taking RISPERDAL® may not have the mental and/or psychological wherewithal to recognize abnormal breast growth as a potential drug adverse event, let alone connect it to RISPERDAL®. For that matter, most patients and/or their parents have no idea what the term "gynecomastia" means, or that it is in any way related to abnormal breast growth.

Additionally, all atypical anti-psychotic medications carry the risk of weight gain. We believe the Prescribing Information for Risperdal® understates and inaccurately minimizes the propensity of RISPERDAL® to cause weight gain. Therefore, when gynecomastia *is* recognized by a patient and/or their healthcare provider, it is often misattributed to diet or nutrition-based weight gain and/or puberty and incorrectly assumed to be unrelated to the patient's ingestion of RISPERDAL®.

On the contrary, between 10-25% of cases of gynecomastia are drug-induced.[7] RISPERDAL® increases prolactin in adolescents more than nearly all other medications. However these facts are not provided to physicians and patients in the Prescribing Information for RISPERDAL®. Were they provided, physicians confronted with adolescent patients on RISPERDAL® who experience abnormal breast growth would reach the unavoidable conclusion that RISPERDAL® had either caused or substantially contributed to the development of that condition. The physician could then take steps, including discontinuing the use of RISPERDAL®, to remedy the gynecomastia.

All of these factors constitute multiple levels at which adverse events can fall through the cracks and fail to be recognized, reported and remedied, permitting the

---

[6] http://www.effexorxr.com/medication-guide.aspx

[7] Braunstein, G.D., Gynecomastia, *N. Engl. J. Med. 1993:328(7); 490-5.*

perpetuation of false safety data, and continued and/or increased sales that result in a vicious cycle of yet more unrecognized and unreported adverse events.

FDA Pediatric Advisory Committee Assessment of the Risperdal® Safety Profile

On November 18, 2008, the FDA's Pediatric Advisory Committee met to consider whether or not to maintain the *status quo* with regard to Risperdal®, or whether a heightened inquiry into the safety of the drug for children was warranted. Specifically, the question posed to the Committee by the FDA was "FDA will continue its standard, ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?"[8]

The Committee "discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects"[9] and unanimously concluded that the *status quo* for Risperdal® was **inadequate**. Specifically, as part of the Committee Vote and Recommendation, "Twelve (12) committee members **unanimously** supported **more than the standard**, ongoing safety monitoring for oral risperidone."[10] Instead, the Committee made several very specific recommendations:

> Twelve (12) committee members recommended the following:
>
> 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. Studies, which may be collaboratively developed with NIH, 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;
>
> 5. Additional evaluation of this class of anti-psychotic medications and concomitant drug use;
>
> 6. Committee is not recommending any public communication before additional discussion which should occur after receipt of data from above recommendations[11]

---

8 *See*: Minutes of The Pediatric Advisory Committee, Tuesday, November 18th, 2008 at page 3 (attached hereto as Exhibit B).

9 *Id.*

10 *Id.* (emphasis added).

11 *Id.* at 3-4 (emphasis added).

Ultimately, the Committee **unanimously** refused to grant its *imprimatur* to Risperdal® as presently labeled, concluding that "Twelve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee."[12]

Three-and-a-half years have passed since the Advisory Committee issued its recommendations. Petitioner is unaware of any evidence that any of the Committee's recommendations have been implemented by the FDA or completed within the intervening 42 months, and the Prescribing Information for Risperdal® therefore remains as it was in November 2008.

The concerns raised by Committee members during their meeting on Risperdal® demonstrate the urgent need for FDA action.

Initially, it should be noted that while the Pediatric Advisory Committee considered a total of nine (9) different "Specific Drug Reviews" during the course of that one-day meeting, their consideration of Risperdal® generated, by far, the most discussion and concern. The Committee's consideration of Risperdal® spans 68 transcript pages and constitutes nearly one-quarter of the transcript pages for "Specific Drug Reviews".

On November 18, 2008, the day of the meeting, the Pediatric Advisory Committee was presented with a "one-year, post-exclusivity adverse event review for risperidone."[13]

Committee Member Dr. Keith Kocis, M.D., M.S. voiced the concern that:

> In looking at this drug compared to many of the drugs that we're going to review or have reviewed over the few years that I've been here, this is somewhat unique in that it's being used – 25 percent of its use has been in pediatrics. It's a drug that has many effects, some that are serious, and I would disagree with your assessment that the FDA is passive in this thing in what they can do.
>
> . . .
>
> And then the final comment is on behalf of the sponsor, in the labeling when they talk about the long-term effects of Risperdal on growth and sexual maturation have not been fully evaluated**, I find that lacking** in the sense that we **know it has profound impact on prolactin** and other endocrine things that I believe should **require them** to study this in children who are undergoing sexual maturation.[14]

Discussing what he characterized as "the very high incidence of hyperprolactinemia in the pediatric population", Committee Member Dr. Geoffrey Rosenthal, M.D., Ph.D. concurred with Dr. Kocis:

---

12 *Id.*

13 *See:* Transcript of 11/18/08 Pediatric Advisory Committee Meeting at p.44 (attached hereto as Exhibit C).

14 *Id.* at pp.74-76 (emphasis added).

If these medications are used to a significant degree in the pediatric population, and there is information regarding the effects of the medication on the neural endocrine access. Is it reasonable to ask the question of what is the long-term effect on growth and development in these areas?[15]

Dr. Rosenthal specifically noted that this concern should be added to the Prescribing Information:

I'm wondering whether there aren't some mechanisms even through the labeling process where particular attention can be drawn to this point, which might then stimulate research in this area . . . and **maybe if particular attention is drawn to the very high occurrence of hyperprolactinemia in the label**, that will raise enough eyebrows that the studies will get done.[16]

When it came time for the Committee to vote, not a single member supported continuation of the *status quo* "standard ongoing safety monitoring":

CHAIRPERSON RAPPLEY: So the vote will be the FDA will continue its standard ongoing safety monitoring for oral risperidone. How many on the Committee support that?

(No response)

CHAIRPERSON RAPPLEY: **So I am not seeing any hands raised.**

. . .

CHAIRPERSON RAPPLEY: So would you like me to summarize our recommendations first before we vote? Okay.

So a summary then of the recommendations that have arisen from our discussion today is that, one, the Committee would like follow-up information regarding **actual use** in light of **concern for extensive and rapidly increasing off-label use of risperidone**.

Number two, that we would **express concern** and like **further information** and further encouragement of **investigation** of **long-term effects** of this medication, including the metabolic syndrome, the other endocrine effects, **in particular, hyperprolactinemia, effects on growth and sexual maturation**.[17]

---

[15] *Id.* at p.79

[16] *Id.* at p.80 (emphasis added).

[17] *Id.* at pp. 93-94 (emphasis added).

FDA Participant Dr. Dianne Murphy, M.D., Director of the Office of Pediatric Therapeutics, OC, reiterated the Committee's concern that the safety profile for RISPERDAL® was lacking:

> You're saying that **we're not finished with looking at adverse effects of these products, particularly this product, in the pediatric population. We have additional concerns**.[18]

Petitioner echoes the Advisory Committee's concern that the current Prescribing Information for RISPERDAL® fails to draw the attention of physicians, patients or the parents of adolescent patients to the "very high occurrence of hyperprolactinemia" in children and the complete absence of safety-data regarding the long-term effects of RISPERDAL® for pediatric patients.

Petitioner's own investigation has revealed that, historically and notoriously, J&J aggressively marketed RISPERDAL® for off-label uses within the pediatric population and took certain steps to affirmatively mislead the medical community and the public at large about the safety of RISPERDAL® for any duration of use. The repercussions of that conduct continue to be manifest in the extensive off-label use of Risperdal® which the Pediatric Advisory Committee raised concerns about in their November 2008 meeting.

Rather than heed the Advisory Committee's recommendation and attempt to assuage their concerns, J&J, through a spokesperson, **summarily dismissed** the Committee's concerns. Specifically, a New York Times article on the Advisory Committee Meeting, headlined Use of Antipsychotics in Children Criticized,[19] quoted a J&J spokeswoman as saying "Adverse drug reactions associated with Risperdal use in approved indications are accurately reflected in the label."

Three-and-a-half years have now passed since the Pediatric Advisory Committee issued its unanimous recommendations and yet the label for RISPERDAL® and the pervasive off-label prescription of the drug remain unchanged. With each passing month thousands of children are exposed to risperidone. Given the explosive growth of the atypical-antipsychotic pediatric market, and the percentages of children with hyperprolactinemia found in the clinical trials as cited in the Prescribing Information, a large number of children have certainly suffered from this serious problem, and many of *those* children have also experienced severe prolactin-related side effects such as gynecomastia

These children could and should have benefited from either another atypical anti-psychotic medication with a better prolactin safety profile, shorter-term use or cycling of their anti-psychotic medication, and/or some other type of intervention.

---

[18] *Id.* at p.100 (emphasis added).

[19] http://query.nytimes.com/gst/fullpage.html?res=9405E3DA1539F93AA25752C1A96E9C8B63&ref=gardinerharris

J&J Hiding Behind A Wall of Confidentiality Orders

Petitioner, through our representation of hundreds of children and adults who have been injured as a result of their ingestion of Risperdal®, have learned of critical documents related to the risks associated with Risperdal® which contradict, complicate and/or substantially call into question the safety data provided by J&J to the FDA. These documents are in J&J's possession and control, and in many instances were generated by J&J and/or its predecessor companies who were involved in the research and development of Risperdal®. Petitioner believes that some of these internal documents have never been reviewed by the FDA, and that others were produced to the FDA buried within "document dumps" of thousands of pages intended to conceal their relevance and significance.

As such, the FDA has been deprived on a more fully-informed, *objective* analysis of this data which is *essential* for the FDA to make a full and fair analysis of the safety profile of Risperdal® and risperidone.

However, J&J has tried to ensure that the evidence in question remain hidden from the FDA by insisting upon confidentiality/protective orders from the Courts overseeing litigation arising from Risperdal®-induced injuries.

In fact, when a specially-appointed panel of "discovery masters", including retired judges, in the New Jersey RISPERDAL® litigation *agreed*, over J&J's vicious *ad hominem* attacks on Petitioner and our clients, that Confidentiality should be lifted so that Petitioner could present the data to the FDA J&J responded by appealing that decision to the trial judge who agreed to allow them to continue to hide the evidence from the FDA.

Nevertheless, J&J remains free to *consent* to Petitioner's presentation of these documents, data, and an expert analysis thereof, to the FDA. FDA must insist that J&J authorize Petitioner to do so in order to counterbalance the biased presentation of the data that J&J has foisted upon the FDA to date. Should the FDA instead request that J&J submit these documents (including internal communications and litigation material such as deposition transcripts) directly to the FDA, Petitioner requests that J&J's document submission be made available for public review and comment, or at the very least be made available to Petitioner for *in camera* review in order to ensure its accuracy and completeness

The Effects of Hyperprolactinemia

While J&J publicly maintains that conditions such as gynecomastia are "mild" and "transient", the experiences of our clients demonstrate that the condition is chronic and devastating.

The development of breasts for even a psychologically healthy adolescent boy or young man can be extremely detrimental. The youngster becomes subject to taunts, derision, and even physical bullying by their peers, as well as questions about their sexual

and gender identity at the very time those elements of their psyche are starting to manifest. For boys and young men who are already mentally and/or psychologically impaired enough to have been prescribed anti-psychotic medications, the daily horror that often accompanies the abnormal development of breasts can be the last straw.

Those of our clients who are otherwise quite functional describe having to avoid peers, miss school, forego social opportunities and the development of relationships, all due to the shame and fear associated with their abnormal breast growth. Having to change their clothes for gym class becomes a regularly-scheduled torture session. While their peers are busy enjoying their summers, playing sports and dating, the victims of RISPERDAL®-induced gynecomastia are hiding at home, under multiple layers of clothing, or bound within home-made compression bands in an attempt to hide the abnormal breasts they have developed.

Indeed, a study presented at the American Academy of Pediatrics Meeting on April 29, 2012 found that being bullied or ostracized increases special-needs children's risk of depression and other internalizing emotional-behavioral conditions.[20] It should be no surprise that the adolescent, teen, and pre-teen boys whom we represent and who have developed breasts as a result of their ingestion of RISPERDAL® uniformly report being bullied (both physically and verbally) and ostracized by their peers. This study now demonstrates the far-reaching consequences of that bullying and ostracism, all caused by an avoidable injury.

Had they known the true risks of RISPERDAL®, these individuals would likely never have agreed to take it, and by and large their physicians would not have prescribed it.

The true devastation of gynecomastia can be recognized by viewing photographs of those suffering this serious condition. Photographs of several young boys who developed gynecomastia as a result of their ingestion of RISPERDAL® are attached to this Petition.[21] Photographs of this type, which demonstrate what gynecomastia is, must be included in the Prescribing Information so that physicians and patients are better informed of the side-effects to look for.

Implications of the Continued Marketing of Risperdal With Inadequate Warnings

J&J has resolutely refused to change its Prescribing Information to more accurately reflect the risk of weight gain, hyperprolactinemia and their associated disorders, which they are authorized to do under the "Changes Being Effected" provision of 21 C.F.R. §314.70(c)(2)(ii).

---

[20] http://www.abstracts2view.com/pas/view.php?nu=PAS12L1_3158&terms; http://aapnews.aappublications.org/content/early/2012/04/29/aapnews.20120429-2

[21] see: *Exhibit D.*

This is despite the fact that, as judge and jury after jury in civil litigation have heard evidence and reviewed internal J&J documents, the courts have found J&J guilty of inappropriate off-label and otherwise fraudulent marketing of Risperdal®.[22]

Specifically, in 2010 J&J was found liable by a jury in Louisiana and ordered to pay a verdict of **$258 Million**.[23] In South Carolina in 2011 J&J was found liable by a judge in a bench trial and ordered to pay a verdict of **$327 Million**.[24] Most recently in 2012 a jury in Arkansas found J&J liable and ordered them to pay a verdict **in excess of $1.1 BILLION**.[25] Also in 2012 J&J was forced to settle a case by the State of Texas for **$158 Million**.[26] These are cases that were brought by the States' Attorneys General seeking to protect the safety of the citizens of their States from J&J's inappropriate conduct related to Risperdal®.

In addition, J&J has been in negotiations with the United States Department of Justice to settle federal civil litigation over the same issues. According to news reports, J&J has offered to pay **$1.3 BILLION** to settle that case. The Department of Justice, having reviewed all of the evidence of J&J's improper marketing of Risperdal®, is said to be insisting upon at least **$2 BILLION** to settle the matter.[27] Such a settlement would also allow J&J to avoid **felony** charges over its marketing of Risperdal®.

And yet, despite the fact that J&J has been ordered by pay over **$1.84 BILLION**, and is in negotiations to pay as much as **$2 BILLION** more, for its inappropriate marketing of Risperdal® they have refused to correct their Prescribing Information. Clearly, J&J considers the children harmed by Risperdal® to be merely a cost of doing business. Indeed, these unprecedented verdicts and settlements constitute just a fraction of the money that J&J has made from Risperdal®. For example, Risperdal® had at least $2.5 Billion in sales in 2007 *alone* (the last year that it enjoyed patent-protection).

Nor does J&J have an incentive moving forward to ensure that the Prescribing Information for Risperdal® accurately reflects the risks associated with the drug. In its 2012 annual report, J&J reported a 10.6% drop in the sales of Risperdal Consta®, the long-acting form of Risperdal®. Sales data were not provided for the standard Risperdal®, but are believed to have been essentially "wiped out" by the sale of generic

---

[22] Petitioner has personally reviewed additional internal J&J documents, that we believe have not yet been either publicly presented in Court or available to the FDA, that suggest that J&J's behavior is even worse than that which has been heard by those Courts or the FDA.

[23] Caldwell ex rel. State of Louisiana v. Janssen Pharmaceutical, 04-C-3967, 27th Judicial Court, St. Landry Parish, Louisiana (Opelousas)

[24] State of South Carolina v. Janssen Pharmaceuticals, 2007-CP-4201438, Circuit Court for Spartanburg County, South Carolina (Spartanburg)

[25] State of Arkansas v. Ortho-McNeil-Janssen Pharmaceuticals Inc., CV07-15345, Pulaski County Circuit Court (Little Rock) Arkansas

[26] Texas v. Janssen LP, D-1GV-04-001288, District Court, Travis County, Texas (Austin)

[27] http://www.businessweek.com/news/2012-03-12/j-and-j-said-to-face-u-dot-s-dot-demand-to-raise-risperdal-settlement-offer; http://online.wsj.com/article/SB10001424052702304441404577478803503320464.html

risperidone.[28] Sales of brand-name Risperdal® in the United States sank an astounding **95.8%** as reported in J&J's 2010 annual report.[29]

Most of these sales have migrated to the generic market. The FDA has given approval to at least 10 companies, including Teva Pharmaceuticals, Mylan Pharmaceuticals and Apotex Corporation, for the manufacture and distribution of generic risperidone

As the ability and/or duty of generic manufacturers to alter the Prescribing Information for generic medications is narrowly circumscribed, the Supreme Court, in the case of Pliva Inc., et al v. Mensing, 131 S.Ct. 2567, 564 U.S. ___ (2011) severely restricted the rights of individuals to avail themselves of the civil justice system to seek relief and compensation for injuries caused by their ingestion of generic drugs such as risperidone.

Therefore, as the Civil Justice system has largely been prevented from acting as an instrument to ensure the safety of generic medications, and as J&J has been unmoved by even enormous verdicts and settlements in cases by the Federal and State governments, unless the FDA steps in to either halt sales of Risperdal® and generic risperidone to children and force J&J to demonstrate both its long-term safety and its efforts to prevent or minimize the off-label use that so concerned the Pediatric Advisory Committee, the vast majority of consumers of this medication, many of whom are adolescents, will be left completely vulnerable to the risks of this drug.

Such a regulatory vacuum is unsafe and unacceptable to the public who rely upon the FDA to protect their children's interests and ensure that the prescription drugs that are approved for sale are safe for their intended purposes.

The Prescribing Information for Risperdal® as presently worded is inadequate for a number of reasons:

* It fails to sufficiently highlight and emphasize the fact that children in particular are especially susceptible to significant increases in prolactin levels triggered by Risperdal®;

* It fails to clearly and completely describe hyperprolactinemia and its associated consequences, including gynecomastia, in a way that is understandable and sufficient for physicians and patients to recognize, report and attempt to remedy the adverse events;

* It fails to recommend routine monitoring of patients for gynecomastia and hyperprolactinemia by, among other things, regular blood tests for prolactin levels and

---

[28] *See*: J&J Profits Rise As Pharma Puts In Steady Performance; *PharmaTimes (http://www.pharmatimes.com/mobile12-04-18/J_J_profits_rise_as_pharma_puts_in_steady_performance.aspx)*

[29] *See*: *PharmaTimes (http://www.pharmatimes.com/mobile/10-04-21/generics_batter_pharma_sales_at_j_j.aspx)*

physical exams by physicians qualified to assess the conditions, to identify and assess abnormal breast growth.

* It fails to acknowledge that the safety data reported therein was derived primarily from adult instead of pediatric patients and after only short-term exposure;

* It includes pediatric indications which are overly broad and susceptible to abuse and off-label use. Specifically, the indication for "irritability" associated with autism is akin to an approval for autism generally, which the FDA refused to give for Risperdal®. Petitioner doubts any autistic child does not demonstrate "irritability" at some point!

* It understates the propensity of the drug to cause weight gain, which can itself contribute to the development of gynecomastia and/or mask that condition and confound physicians' ability to make an accurate diagnosis

* It fails to acknowledge the conflicts of interest and other factors which demonstrate the bias and lack of objectivity in the published literature used by J&J to promote the drug.

* It significantly understates the propensity of RISPERDAL® to trigger gynecomastia in children by stating an incidence of 2-3% when in fact the true incidence with typical long-term use is 5%.

* It fails to warn that gynecomastia will most likely be permanent if present for one year or more.

* It fails to state that prescribing Risperdal during puberty and/or after weight gain will significantly exacerbate and increase the risk of permanent gynecomastia.

* It fails to state that there are numerous other agents that do not cause as much weight gain and do not increase prolactin.

* It fails to state that almost all children given Risperdal will have raised prolactin and this is dangerous for their health.

* It fails to state that prolactin is raised also within what are described as "normal" ranges but that the drug should be stopped if there is an increase of prolactin within the so-called normal ranges since normal for adults is different for children.

* It fails to recommend that physician who prescribe RISPERDAL® to adolescent patients closely monitor their patients' prolactin levels and routinely examine their patients for abnormal breast growth and impaired sexual maturation and to consider discontinuing RISPERDAL® at the first sign of any of those signs and/or symptoms.

* J&J has never done the long-term study requested by the FDA advisory committee in 2008.[30] For this reason, until such a study is done, the approval of Risperdal and Invega for use in children and adolescents should be prohibited.

Summary of Requested Action

For all of the reasons set forth above, Petitioner respectfully requests that the FDA **immediately revoke approval of Risperdal, Invega, and all generic version of risperidone for use in children unless and until J&J presents evidence supporting: safety of long-term use of the drug; and efforts on their part to prevent the off-label prescription of Risperdal to patients for whom those risks do not outweigh the potential benefits of treatment and otherwise satisfy the concerns of the FDA's Pediatric Advisory Committee; and either voluntarily submit their internal communications and documents as well as litigation documents related to Risperdal or consent to Petitioner's presentation of our own *objective* presentation on these issues to counter-balance J&J's own biased presentation.**

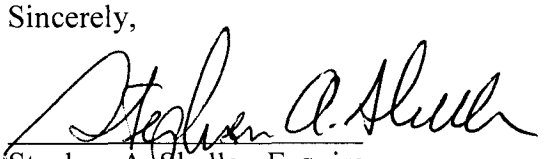
Environmental Impact Statement

Nothing requested in this Petition will have an impact on the environment.

Certification

We certify that, to the best of our knowledge and belief, this Petition includes all information and views on which this Petition relies, and that it includes representative data and information known to the Petitioners which are unfavorable to this Petition.

Sincerely,



Stephen A. Sheller, Esquire
SHELLER, P.C.
1528 Walnut Street, 4th Floor
Philadelphia, PA 19102
(215) 790-7300
(215) 546-0942

[30] While J&J purported to address the issue in its RIS-NAP-4022 study, issued on 12/28/11, this study was terminated early due to failure to reach enrollment targets and by J&J's own admission, "the low enrollment resulted in an underpowered study." Nevertheless, this study confirmed that Hyperprolactinemia occurs significantly more often with Rispderdal than other atypical anti-psychotics (25.6% vs. 2%).

From: (215) 790-7300
Albert J. Brooks, Jr., Esquire
SHELLER LUDWIG
1528 Walnut Street, 4th Floor

Philadelphia, PA 19102

Origin ID: MUVA

FedEx Express

J1220120718O325

Ship Date: 27JUL12
ActWgt: 1.0 LB
CAD: 3519404/INET3300

Delivery Address Bar Code

Ref # 201991 (Risperdal)
Invoice #
PO #
Dept #

SHIP TO: (301) 827-6860 BILL SENDER

Division of Dockets Management
Food & Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

MON - 30 JUL A2
PRIORITY OVERNIGHT

TRK# 0201 7986 6907 7498

K8 OBTA

20852
MD-US
IAD

515G1/E052/AA44

After printing this label:
1. Use the 'Print' button on this page to print your label to your laser or inkjet printer.
2. Fold the printed page along the horizontal line.
3. Place label in shipping pouch and affix it to your shipment so that the barcode portion of the label can be read and scanned.

Warning: Use only the printed original label for shipping. Using a photocopy of this label for shipping purposes is fraudulent and could result in additional billing charges, along with the cancellation of your FedEx account number.
Use of this system constitutes your agreement to the service conditions in the current FedEx Service Guide, available on fedex.com.FedEx will not be responsible for any claim in excess of $100 per package, whether the result of loss, damage, delay, non-delivery,misdelivery,or misinformation, unless you declare a higher value, pay an additional charge, document your actual loss and file a timely claim.Limitations found in the current FedEx Service Guide apply. Your right to recover from FedEx for any loss, including intrinsic value of the package, loss of sales, income interest, profit, attorney's fees, costs, and other forms of damage whether direct, incidental,consequential, or special is limited to the greater of $100 or the authorized declared value. Recovery cannot exceed actual documented loss.Maximum for items of extraordinary value is $500, e.g. jewelry, precious metals, negotiable instruments and other items listed in our ServiceGuide. Written claims must be filed within strict time limits, see current FedEx Service Guide.