

**Some critics of Janssen, including plaintiff’s lawyers, have stated it is improper for Risperdal to have been used to treat elderly dementia patients. As you consider that position, we suggest you consider the following:**

- The Psychopharmacological Drugs Advisory Committee (“PDAC”) which recommended the approval of Risperdal noted:
  - “Remember, anti-psychotic drugs...are going to be used in a lot of other people other than schizophrenics. I would expect a big medical use. A use in nursing homes.” (Dr. Paul Leber, head of the Division of Neuro-pharmacological Drug Products -- the division within the FDA responsible for the approval of antipsychotic drugs)
  - “In terms of use in geriatric populations, isn’t it true that...if you have a psychotic geriatric person, if the person does not get [Risperdal], he or she is going to get something else...It is a matter of alternatives. I mean I do not see anything in these data that would indicate that this drug is any more dangerous and possibly less dangerous in geriatric populations.” (Dr. Robert Mark Hamer, PDAC member)
- Dosing and risk information for elderly patients has appeared on the Risperdal label since approval in 1993, including .50 mg dosing for the elderly in the original product label:
  - “DOSAGE AND ADMINISTRATION...Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly...”
- Even today, the FDA approved label specifically addressed geriatric use:
  - “In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.”
- The 2009 Centers for Medicare and Medicaid Services State Operations Manual provides for use of Risperdal in elderly dementia patients in long-term care facilities:

Antipsychotic medications	
<p>All classes, e.g.,</p> <p>First generation (conventional) agents, e.g.</p> <ul style="list-style-type: none"> <li>• chlorpromazine</li> <li>• fluphenazine</li> <li>• haloperidol</li> <li>• loxapine</li> <li>• mesoridazine</li> <li>• molindone</li> <li>• perphenazine</li> <li>• promazine</li> <li>• thioridazine</li> <li>• thiothixene</li> <li>• trifluoperazine</li> <li>• triflupromazine</li> </ul> <p>Second generation (atypical) agents, e.g.</p> <ul style="list-style-type: none"> <li>• aripiprazole</li> <li>• clozapine</li> <li>• olanzapine</li> <li>• quetiapine</li> <li>• risperidone</li> <li>• ziprasidone</li> </ul>	<p><b>Indications</b></p> <ul style="list-style-type: none"> <li>• An antipsychotic medication should be used only for the following conditions/diagnoses as documented in the record and as meets the definition(s) in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Training Revision (DSM-IV TR) or subsequent editions): <ul style="list-style-type: none"> <li>○ Schizophrenia</li> <li>○ Schizo-affective disorder</li> <li>○ Delusional disorder</li> <li>○ Mood disorders (e.g. mania, bipolar disorder, depression with psychotic features, and treatment refractory major depression)</li> <li>○ Schizophreniform disorder</li> <li>○ Psychosis NOS</li> <li>○ Atypical psychosis</li> <li>○ Brief psychotic disorder</li> <li>○ Dementing illnesses with associated behavioral symptoms</li> <li>○ Medical illnesses or delirium with manic or psychotic symptoms and/or treatment-related psychosis or mania (e.g.,</li> </ul> </li> </ul>

**Daily Dose Thresholds for Antipsychotic Medications Used to Manage Behavioral Symptoms Related to Dementing Illnesses**

Generic Medication	Dosage
<b>Second Generation</b>	
aripiprazole	10 mg
clozapine	50 mg
olanzapine	7.5 mg
quetiapine	150 mg
risperidone	2 mg
ziprasidone	*

\* Not customarily used for the treatment of behavioral symptoms

(See Appendix PP, CMS Medicare State Operations Manual, Rev. 52, June 12, 2009, pgs. 379-85) (See also, Appendix PP, CMS Medicare State Operations Manual, Rev. 133, February 6, 2015, pgs. 432-41)

- A 2001 HHS-OIG report recognized the use of Risperdal in elderly dementia patients:

- Among nursing home residents “on antipsychotic drugs, the most common diagnosis is dementia with associated psychotic or agitated behaviors.” (Nov. 2001 HHS-OIG Report “Psychotropic Drug Use in Nursing Homes”)
- “Antipsychotic medications are used to treat various psychoses and neurologic conditions... Other indications for long-term anti-psychotic use in the elderly are organic mental syndromes (including dementia with associated psychotic and/or agitated features defined by “certain behaviors” that are harmful to self or others) and mood disorders with psychotic features.”
- “Eighty-five percent of residents’ psychotropic drug use is medically appropriate. Nearly all have the potential to benefit functionally from their drug therapy and are using the drugs within Medicare guidelines for appropriate use.”

**Some critics, including plaintiff’s lawyers, have stated that use of Risperdal to treat pediatric patients is not appropriate. As you assess that position, we suggest you consider the following:**

- As recognized by the American Academy of Child and Adolescent Psychiatry (“AACAP”), informed use of psychotropic drugs has positively impacted children and adolescents.<sup>1</sup> As such, AACAP has recommended antipsychotics as first-line treatment for both schizophrenia and bipolar mania in children and adolescents since 2001.<sup>2</sup>
- In September 2000, the National Institute of Mental Health recognized that “[p]sychotropic medications may be prescribed for young children with mental, behavioral, or emotional symptoms when the potential benefits of treatment outweigh the risks. Some problems are so severe and persistent that they would have serious negative consequences for the child if untreated . . . .”<sup>3</sup>
- Risperdal was the first atypical antipsychotic to obtain indications for use in the pediatric population. In December 2006, FDA approved Risperdal to treat irritability associated with autism. In addition, FDA granted Risperdal pediatric exclusivity in March 2007 and subsequently (in August 2007) approved Risperdal for the treatment of schizophrenia in

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<sup>1</sup> American Academy of Child and Adolescent Psychiatry, *Policy Statement for Pharmaceutical Benefit Management and the Use of Psychotropic Medication for Children and Adolescents* (2009).

<sup>2</sup> American Academy of Child and Adolescent Psychiatry, *Practice Parameters for the Assessment and Treatment of Children and Adolescents with Schizophrenia* (2001); American Academy of Child and Adolescent Psychiatry, *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder* (2007).

<sup>3</sup> NIMH, *Treatment of Children with Mental Disorders* (September 2000)

adolescents ages 13 to 17 and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17.<sup>4</sup>

- In approving Risperdal for the irritability associated with autistic disorders in 2006, FDA announced: “This approval should benefit many autistic children as well as their parents and other care givers. Our agency strongly encourages the development of appropriate pediatric labeling for adult drugs, and *Risperdal is a welcome addition to the growing number of such products that have been shown to have an appropriate risk-benefit profile when tested in children.*”<sup>5</sup>
- When approving the pediatric schizophrenia and bipolar mania indications, FDA acknowledged: “The pediatric studies of Risperdal provided an opportunity to assess the effectiveness, proper dose, and safety of using this product in the pediatric population. . . These data have permitted the identification of the effective pediatric dose ranges and have provided an evidence-based approach for treating these disorders in pediatric patients.”<sup>6</sup>
- In a public letter dated November 25, 2014, the FDA stated:
  - “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.”<sup>7</sup>
  - “Before the approval of each pediatric indication for Risperdal and Invega, the [FDA] determined that sufficient short-term and long-term safety information to support approval had been presented by the drug sponsor. . . . [B]ased 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

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<sup>4</sup> Abilify – schizophrenia (October 2007), bipolar (February 2008); Seroquel & Zyprexa – schizophrenia (December 2009), bipolar (December 2009).

<sup>5</sup> FDA Press Release (October 6, 2006) (emphasis added).

<sup>6</sup> FDA Press Release (August 22, 2007).

<sup>7</sup> Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Stephen A. Sheller, Esq., Sheller, P.C. 5 (November 25, 2014).

which the applications were approved that would warrant revocation of the pediatric indication of these drugs.”<sup>8</sup>

- “The risks of treatment with these drug products, including the risks with which your petition is principally concerned, are well known. Gynecomastia is a common clinical manifestation of hyperprolactinemia, regardless of cause, 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.”<sup>9</sup>

**To the extent critics have suggested that sharing information about off-label use is wrong please consider the FDA’s position reflected in the following citations:**

- “The 2009 guidance, consistent with the objectives of section 401 of FDAMA (which was no longer law), recognized that the public health may benefit when health care professionals receive truthful and non-misleading scientific or medical publications on unapproved new uses. This information can be particularly important given that a health care professional can generally choose to use or prescribe an approved or cleared medical product for an unapproved use, if the off-label use is appropriate based on his or her judgment.” (p. 6)
- “Although this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses, it also continues to recognize that this information is in no way a substitute for the FDA premarket review process, which allows FDA to be proactive, rather than reactive, in protecting the public from unsafe or ineffective medical products.” (p. 6-7).
- Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (DRAFT) (Dec. 2011) (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf>)

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<sup>8</sup> Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Stephen A. Sheller, Esq., Sheller, P.C. 3-4 (November 25, 2014).

<sup>9</sup> Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Stephen A. Sheller, Esq., Sheller, P.C. 7-8 (November 25, 2014).

- “[O]nce a drug or medical device has been approved or cleared by FDA, generally, health care professionals can lawfully use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). FDA recognizes that these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care.” (p. 2).
- “Scientific or medical departments within drug or medical device firms often maintain a large body of information about their products. This information typically includes data and other information consistent with the approved or cleared indications or conditions of use for their products, but may also include off-label information for their products. As noted, although dissemination of off-label information can be used as evidence of new intended uses for products in distribution, such information may also be of use to individuals seeking information about a medical product for themselves, patients, family members, or friends.” (p. 2-3).
- “FDA recognizes that firms are capable of responding to requests about their own named products in a truthful, non-misleading, and accurate manner. Furthermore, as these firms are regulated by FDA and have robust and current information about their products, FDA recognizes that it can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses of the firm’s products that are addressed to a public forum, as other participants in the forum who offer responses may not provide or have access to the most accurate and up-to-date information about the firm’s products.” (p. 3).