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Quick Pulse

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FDA Approves Risperdal for Children and Adolescents

On August 22, 2007, the FDA approved the first atypical antipsychotic – Johnson & Johnson's Risperdal (risperidone) – for use in children and adolescents with two psychiatric disorders. The drug is now labeled for:

- Treatment of **schizophrenia** in adolescents age 13-17.
- Short-term treatment of manic or mixed episodes of **bipolar I disorder** in children and adolescents age 10-17.

This is the first FDA approval of an atypical antipsychotic drug to treat either disorder in these age groups, though lithium is approved to treat adolescent bipolar disorder. In making the announcement about the approval, Dr. Thomas Laughren, director of the FDA's Division of Psychiatry Products, Center for Drug Evaluation and Research (CDER), emphasized that these are very serious and disabling psychiatric disorders, "Schizophrenia is a serious disorder characterized by hallucinations, delusions, and disorganized thinking. Bipolar disorder, also known as manic-depressive illness, is a serious psychiatric disorder characterized by wide shifts in a person's mood, energy, and ability to function."

The FDA estimates that from 0.1% to 1% of newly diagnosed schizophrenics are in this younger age group. Dr. Laughren said, "It is a small number of new onset cases of schizophrenia…but it sometimes begins in this young age group even though more typical onset is later…Some clinicians say they can diagnose it down to age 10…Because of the difficulty of diagnosis, we focused on ages 13-17…It is clearly a problem in this age group." Dr. Dianne Murphy, director of the FDA's Office of Pediatric Therapeutics, added, "The majority of patients who have these severe diseases is not a high percentage in this young population, but it is a devastating phenomenon for the family…This is a public health issue. There are children and families who are devastated by these diseases."

The FDA first approved Risperdal in 1993 for the treatment of schizophrenia in adults. It was later approved for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and last fall the FDA approved Risperdal for the treatment of irritability associated with autistic disorder in children and adolescents 5 to 16 years old.

Risperdal and other atypical antipsychotics have been commonly used off-label in pediatric patients, and five years ago, the FDA asked all of the manufacturers to test their drugs in children and adolescents as part of its pediatric drug development initiative. J&J was the first to complete and submit those trials, and it will get an additional period of marketing exclusivity as a result, but other companies have trials that are underway or near completion, so the FDA expects to be reviewing data from other atypical antipsychotics over the next few months or years. The Risperdal approval is for the oral formulation only, not the long-lasting injectable Risperdal Consta.

The pediatric approval of Risperdal is based on three short-term, double-blind, randomized, placebo-controlled trials – two in schizophrenia and one in bipolar disorder – with a total of 300-400 patients.

- **Schizophrenia.** Two short-term (6- to 8-week) studies were conducted in adolescents experiencing an acute episode of schizophrenia at the time of enrollment. The study found that treated patients generally had fewer symptoms, including a decrease in hallucinations, delusional thinking, and other symptoms of their illness.
- **Bipolar disorder.** One 3-week trial in children or adolescents with bipolar I disorder who were experiencing a manic or mixed episode found that treated patients generally had fewer symptoms, including a decrease in their elevated mood and hyperactivity, and other symptoms of their illness.

The studies also found that a lower dose (1-3 mg) of Risperdal is as effective as a higher dose (3-6 mg). FDA officials described this as an important finding. Dr. Laughren said, "There didn't appear to be any added efficacy of high vs. low dose (Risperdal), and we think that is important information to provide to prescribers…That dose (1-3 mg) is slightly lower than that used for adults…The higher doses are associated with more adverse events…and, on average, the lower doses did as well as the higher doses." Dr. Murphy added, "It is really important to know that using a higher dose in kids will not increase efficacy...If anything, it will probably increase adverse events."

FDA officials insisted that the benefits of Risperdal outweigh the safety concerns – and there are safety concerns, including:

- **Weight gain, metabolic syndrome, and obesity.** Dr. Laughren said, "There are some data coming from these trials on weight gain suggesting there is a signal for some weight gain with this drug, and that is characterized in the labeling…These were relatively short trials, but there were some children who took it up to a year, and we saw some weight gain, but no indication of diabetes…The labeling will reflect the new information that was discovered in terms of weight gain in pediatric patients. The drug already has a very strong warning statement, and that applies to children as well as adults…but the new information on weight gain is reflected in the label."
- **Diabetes.** Dr. Laughren said, "The label for Risperdal does have a very prominent warning about the risk of diabetes, and that is something we will be looking at. We didn't really see in these relatively short-term trials any signal of lack of regulation of glucose, which is a precursor for diabetes, but one would have to have longer studies."
- **Prolactin elevation.** Dr. Laughren said 49% of pediatric patients on Risperdal had elevated prolactin vs. 2% of placebo patients, "Clearly prolactin elevation is an adverse finding associated with this drug…This is not new information…This was also clearly recognized in adults …So, we are seeing a signal for a fairly robust increase in prolactin…We think it is fairly prominently labeled…We think physicians are well aware of this problem…Both of these disorders are very serious, and the decision to use these medications is not taken lightly by a clinician… Those clinicians and families have to weigh the risks and the benefits…It is very serious and has to be treated… There are some risks with these medications, no question about that."
- **Pituitary tumors.** Dr. Laughren said, "That is an issue we are keenly interested in, and we are evaluating it through several databases. We won't have an answer for some time...but it is an issue we are very interested in looking at."

While these issues are being watched, the benefits outweigh the risks, FDA officials insisted. Dr. Laughren said, "I'm not aware there is over-utilization in these populations…We are concerned about the safety profile of these drugs and are very closely looking at post-marketing data for this and other drugs in pediatric patients and waiting for that data, and we will make additional labeling changes if we think that is appropriate…For these indications, given the side effect profile, it is a relative thing…These drugs do have some significant side effects, but they are quite predictable…And what we are seeing in pediatrics is something quite similar to what is seen in adults…And we draw assurance from that that there is nothing unique occurring in pediatrics…We have huge experience in adults with these disorders…One issue of great interest is the effects the drug might have on growth and development, and we asked the company to do a longer-term study in pediatrics to look at those issues – weight, growth hormones, and prolactin over a longer period of time, and that study is ongoing…We expect to generate additional information that might be useful."

There will not be a black box warning about either weight gain or diabetes. The FDA plans to monitor the longer-term safety of Risperdal in pediatric patients. Dr. Laughren said, "The drug was approved for irritability in autism last fall, and as part of that we asked the company to do a much longer trial to look at weight gain and glucose, and that study is underway."

Why didn't the FDA hold an advisory committee meeting on this pediatric approval? Dr. Laughren said, "We didn't feel we needed additional advice…The questions were pretty straightforward…On diabetes and metabolic risk we didn't think the information was sufficiently different from other programs to justify taking this to an advisory committee…We can't take every application to an advisory committee or we would spend all our time in advisory committees. We felt we could make this particular decision without the advice of an advisory committee."

Will additional post-marketing studies be required for Risperdal in children? No, nothing additional was required for this approval. ♦