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FOX 5 Investigates: Singulair

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WASHINGTON - Kids so out of control, you can't take them to church, the movies or even the mall. The problem may not be the kid or even their parents, but instead a popular drug prescribed to millions of kids across the country.

Singulair is drugmaker Merck's number one selling drug, bringing in $4.6 billion last year. Doctors call it a miracle drug because it keeps kids with severe asthma and allergies out of the emergency room.

But there are a growing number of parents who say the risks associated with the drug could outweigh its benefits.

For kids with asthma, there's nothing more exciting than running, especially when you're trying to catch your big sister.

When he was just two years old, Willy Epperly started taking the asthma-allergy drug Singulair.

"We thought it was just a normal 'terrible twos' kind of thing," said Willy's mother Melissa.

She says in the beginning, it was subtle.

"By the time he got to pre-kindergarten, he was pushing children. He was yelling at the teacher. He wasn't sitting still. He wasn't following directions," said Melissa. "I was literally afraid he was going to be kicked out of school."

Even Willy, who is now five years old, felt something wasn't right.

"I got really mad at my body," he said. "I tried to stop my body from doing bad things. I told it to stop, but it kept on doing it."

When doctors told Melissa her son might have ADHD and might need even more medication, she decided to re-read Singulair's packaging and discovered side-effects had been added in the years Willy was on the drug. Aggressive behavior, hostility, hallucinations, night-terrors, tremors, irritability, anxiety, depression and even suicide.

Read Singulair's Complete Label
Read Singulair's Patient Information Leaflet

"I was like, 'Oh my God!'" Melissa said. "This is exactly what this is."

"Children are not small adults," said Dr. Anne Zajicek, a pediatric pharmacologist at the National Institute of Child Health and Human Development. "The fact they are developing makes them completely different. The way they absorb drugs, the

way they clear drugs, the way their liver metabolizes drugs, the way their kidneys clear drugs is all, for at least school age children, considerably faster than adults."

She says it can be hard to diagnose behavioral side effects in small children because parents don't always know the difference between normal growing pains and serious side effects.

After ruling out dosing mistakes **(watch VIDEO #3 to understand why a teaspoon isn't always a teaspoon)**, Dr. Zajicek says parents can help doctors with an accurate diagnosis by keeping a daily log of their child's behavior before and after they start using any type of drug. And if possible, catch it on video.

That's what Ilene Goldman did when she started noticing her twins, Liam and Jake, behaving badly. She says at first, they were hyperactive and anxious. But then Liam started to shake. Pointing to a home video she took, Ilene says Liam "was tremoring and squeaking and just making all of these funny noises and rolling his eyes. I would say to him, 'Why are you doing that?'" She says Liam would always respond, "I don't know."

Ilene says doctors were convinced Liam had developed the neurological disorder Tourette Syndrome until she took both boys off Singulair. That's when she says their symptoms disappeared.

"They started having these problems on the drug," said Dr. Sidney Wolfe. "When they were taken off the drug, they got better. That's a hallmark of a drug-induced illness."

Wolfe is the author of "Worst Pills, Best Pills" and lists Singulair as a "Do Not Use" drug.

"Children haven't been adequately studied for a lot of drugs and yet, because of heavy promotional campaigning, they wind up being treated with a number of drugs that have really questionable benefits," said Dr. Wolfe.

He says millions of kids are put on Singulair instead of other asthma-allergy drugs because Merck, the company that makes Singulair, has launched an aggressive marketing campaign.

For instance, Merck teamed up with kid-friendly groups like Scholastic Press and by giving money to the American Academy of Pediatrics to train doctors on "diagnosing" and prescribing "proper medication" for asthma.

Click on the links to read Scholastic's statement and the American Academy of Pediatrics statement

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"I mean the drug companies don't spend $52 billion a year advertising and promoting drugs just because the like to give money away," Wolfe said. "It works."

Pamela Eisele is a spokeswoman for Merck and says "we are confident in the safety of Singulair." She says the company conducted clinical trials on more than 2,700 children and while the tests, "were not specifically designed to identify behavioral side effects, such events were recorded as adverse events." Since they could be "possibly related" to Singulair, Eisele says "we elected to put in the labeling." **(Click here to view the FDA's statement)**

As for the Epperlys, they joined the

website **www.parentsforsafety.org** and are trying to tell as many parents as they know about their experience with Singulair. After consulting with Willy's doctor, Melissa says she took him off Singulair and put him on a different asthma medication.

"The first week he was off it, he said 'excuse me' and I was like, 'What did you do with my child?' You've never said 'excuse me' before!" said Melissa.

And then, just as she started to explain how she never worries about Willy's outbursts anymore, Willy raised his hand and waited, arm stretched, until his mother finished.

"Excuse me," he said. "Can I go upstairs?"

And that, Melissa whispered, says it all.

Scholastic's Statement

Parent & Child is a magazine for parents; there is no content in the magazine that is directed at children. At Parent & Child, we take our responsibility as a trusted resource for busy working parents very seriously and are sensitive to parental concern about the side effects of Singulair or any drug. With this in mind, we follow strict guidelines and restrictions for conveying the safety information that consumers should consider, in consultation with a medical professional, before taking or administering the medication. In this case, the safety information for Singulair is displayed in three places in the four-page insert. It appears prominently in standard-sized print on page 3 and page 4 and, in addition, in the highly detailed foldout containing patient information and physician prescribing information that is attached. We feel confident that readers will not easily disregard or overlook these issues as they read through the insert.

Kyle Good
Vice President, Corporate Communications
Scholastic Inc.

American Academy of Pediatrics' Statement

The American Academy of Pediatrics (AAP) Comprehensive Asthma Program is an independent program promoting the evidence-based guidelines for asthma care from the National Heart, Lung, and Blood Institute (NHLBI). The incidence of asthma in children – especially minority children living in poverty – is steadily increasing. The goal of this program is to improve the care of children with asthma by helping pediatricians adopt the NHLBI guidelines in their practices, within the context of a medical home, thereby reducing the rates of emergency department visits, hospitalizations and deaths in children with uncontrolled asthma.

An educational grant to provide funding came from the Merck Childhood Asthma Network Inc., a non-profit, 501(c)(3) organization that is headed by Dr. Floyd Malveaux, and that is separate from Merck & Co. The grant provides $651,530 from 2008 through 2011. While the sponsor provided funding for the Comprehensive Asthma Program through an educational grant, the content is determined solely by the AAP using guidelines from the NHLBI. It is not a conflict of interest. By accepting external grants like this, the AAP is able to disseminate its educational messages to mass audiences.

Merck's Statement

WHITEHOUSE STATION, N.J., OCT. 26, 2010 – Merck & Co., Inc. provided the following statement regarding the safety of SINGULAIR® (montelukast sodium).

Nothing is more important to Merck than the safety of our medicines and vaccines and the people who use them. We are confident in the efficacy and safety of SINGULAIR, a medicine that has been prescribed to tens of millions of patients with asthma or allergic rhinitis since its approval more than 12 years ago.

In 2009, Merck worked with the FDA to promptly update the "Precautions" section of the prescribing information for SINGULAIR to reflect reports of behavior and mood-related events in adult, adolescent and pediatric patients taking SINGULAIR. Since the introduction of SINGULAIR in 1998, Merck has updated the prescribing information for SINGULAIR to communicate a range of adverse events reported with post-marketing use of the medicine, including the types of behavior and mood-related events noted in the Precautions section.

Merck continues communicating with patients, parents and healthcare providers about SINGULAIR in ways that help inform their decisions about appropriate treatment choices. We encourage patients and parents of children with asthma or allergies to talk with their healthcare providers if they have any questions about the benefits and risks of SINGULAIR. Patients, or parents of children who are patients, should talk to their healthcare providers before starting or stopping treatment with any prescription medicine.

For the millions of people suffering from either asthma or allergic rhinitis, SINGULAIR is an important treatment option for appropriate patients.

SINGULAIR is a prescription medicine used to prevent asthma attacks and for long-term treatment of asthma in adults and children 12 months and older; and for relief of symptoms of indoor and outdoor allergies (outdoor allergies in adults and children as young as 2 years and indoor allergies in adults and children as young as 6 months).

U.S. Food and Drug Administration's

Statement

1. Is the FDA currently doing any investigations/reviews of Singulair? If so, what is the FDA looking at?

FDA cannot comment on whether it is currently doing any investigations or reviews of Singulair. In 2009, FDA completed a review of leukotriene modifiers (including Singulair) and the potential risk of neuropsychiatric side effects and updated the product labels accordingly. That information can be found here:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm
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In addition, FDA routinely reviews adverse event reports submitted to the FDA Adverse Event Reporting System and other data streams as part of the agency's postmarketing safety surveillance programs. If a signal of a serious risk is identified, FDA conducts appropriate investigations and may communicate to the public about the new or emerging risk.

2. Singulair is prescribed to both adults and children. Are there special criteria the FDA considers when it reviews drugs for small children? a. What kind of special concerns are there? No base-line for behavioral problems? Inability to vocalize problems? Smaller bodies? Long-term developmental problems?

Pediatric patients often differ from adults in not only their size, but also in the way that they metabolize and respond to medications. In addition, special safeguards must be put into place when children are being enrolled in clinical trials. Due to these reasons, separate studies are often conducted in the pediatric population to address dosing, safety, and efficacy. The FDA has authority to require studies of certain medications under the Pediatric Research Equity Act. The FDA will evaluate if additional preclinical information is needed before studies can begin in children with the disease or condition of interest, and then the FDA evaluates what additional information is needed to label the product for use in pediatric populations.

3. How does a side-effect warning come into being? Can the FDA "force" a company to put a side-effect onto its labeling? Or is it entirely voluntary?

After approval of a drug, additional side effects may be identified based on new clinical data or spontaneous reports of serious side effects to the manufacturer or to FDA's Adverse Events Reporting System. Manufacturers can add new safety information to a drug's label on their own initiative. FDA reviews all proposed labeling changes to ensure they are adequately supported by the available data. Under new authority provided by the Food and Drug Administration Amendments Act (FDAAA) of 2007, FDA can also require drug sponsors to make safety-related labeling changes in certain cases.

4. What are the rules when a side-effect is added to a drug like Singulair? Does the FDA issue an alert? Are pharmacies and doctors required to notify patients? Or is the burden on the patient?

There are no set rules regarding notification of pharmacies, doctors, and patients when additional safety information is added to a product label. Each labeling change is handled on a case-by-case basis, depending upon its significance. FDA may issue an alert to raise awareness of the new safety information added to the labeling, or may require the manufacturer to communicate information about the safety label change, or the manufacturer may provide information to healthcare providers voluntarily.

5. Over the last decade, Singulair has slowly added neuropsychiatric side-effects to its labeling…initially there weren't any…now it runs the gamut from anxiety to suicide. Is it common or uncommon for side-effects to slowly be added to medications as time goes by?

It is not unusual for side effects to be added to a product label over time as more is learned about the drug, either from additional clinical trial data or spontaneous adverse event reporting. FDA regulations require manufacturers to continually review available safety information and update the label in a timely manner as new information becomes available.

6. Some of the parents we are talking to are calling for the FDA to add a "black box" warning so doctors/patients will take the possible side-effects seriously. What does it take for the FDA to consider/add this kind of labeling? Is the FDA considering it as we speak? If so, what are the concerns? What has to be balanced?

FDA regulations describe when a boxed warning may be required. The regulations state, "Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box.

The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word ``WARNING'' and conveys the general focus of the information in the box.

The box must briefly explain the

risk and refer to more detailed information in the ``Contraindications'' or ``Warnings and Precautions'' section, accompanied by the identifying number for the section or subsection containing the detailed information."(21 CFR 201.57(c)(1))

Generally, a Boxed Warning is required to highlight a drug reaction so serious in proportion to the potential benefit from the drug (e.g., death, life-threatening event or permanent disability) that it is essential it be considered in assessing the risks and benefits of using a drug, or to highlight a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug.

As stated in the response to question 1, FDA does not comment on pending investigations or reviews, but will communicate with the public about emerging safety information when appropriate, and at the completion of a significant review.

7. What does it take for side-effects to outweigh the benefits of a drug? For instance, what tipped the scale for Vioxx or other drugs that have been pulled off the market?

All drugs carry risks as well as benefits. Benefit versus risk is evaluated during the FDA drug review process, and benefits must outweigh risks for a drug to receive FDA marketing approval. The FDA realizes that when an approved new drug becomes widely used in clinical practice, health care professionals may observe differences from clinical trial results in both the incidence and/or types of adverse drug experiences. After approval of a new drug, the sponsor is required to provide periodic summary reports of adverse events to the FDA, as well as individual reports of any serious adverse reactions. The Agency monitors these reports to determine if any safety problems or trends can be identified and takes action accordingly. These are case-by-case decisions based on a careful review of the available data of the risk vs. benefit profile of a drug.There is no formula for assessing the risk vs. benefit profile. That assessment may change over time as more is known about a drug. Vioxx was withdrawn voluntarily by the manufacturer due to safety concerns. Additional information regarding Vioxx can be found at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm