U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis

Risks may include suicidal thoughts or actions

3-4-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?
The U.S. Food and Drug Administration (FDA) is strengthening existing warnings about serious behavior and mood-related changes with montelukast (Singulair and generics), which is a prescription medicine for asthma and allergy.

We are taking this action after a review of available information led us to reevaluate the benefits and risks of montelukast use. Montelukast prescribing information already includes warnings about mental health side effects, including suicidal thoughts or actions; however, many health care professionals and patients/caregivers are not aware of the risk. We decided a stronger warning is needed after conducting an extensive review of available information and convening a panel of outside experts, and therefore determined that a *Boxed Warning* was appropriate.

Because of the risk of mental health side effects, the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines. For allergic rhinitis, also known as hay fever, we have determined that montelukast should be reserved for those who are not treated effectively with or cannot tolerate other allergy medicines. For patients with asthma, we recommend that health care professionals consider the benefits and risks of mental health side effects before prescribing montelukast.

What is FDA doing?
We are requiring a *Boxed Warning*, our most prominent warning, to be added to the prescribing information of montelukast to describe these serious mental health side effects and to recommend that montelukast should only be reserved to treat allergic rhinitis in patients who are not treated effectively with or cannot tolerate other allergy medicines. We are also requiring a new patient Medication Guide to educate patients and parents/caregivers about the medicine.

What is montelukast and how can it help me?
Montelukast is FDA-approved for asthma and allergies. It is a prescription medicine approved to prevent asthma attacks and for long-term treatment of asthma in adults and

children 1 year and older. It is also approved to prevent exercise-induced asthma in patients 6 years and older. In addition, it is approved to help control the nasal symptoms of seasonal outdoor allergies in patients 2 years and older and year-round indoor allergies in those 6 months and older. Montelukast works to help improve symptoms of asthma and allergic rhinitis by blocking substances in the body that may cause them. Montelukast was first approved by FDA in 1998. It is marketed under the brand name Singulair and as generics.

What should patients and parents/caregivers do?

Patients and parents/caregivers should stop montelukast and discuss with a health care professional right away if you or your child experience behavior or mood-related changes while taking the medicine. These may include:

• agitation, including aggressive behavior or hostility • attention problems • bad or vivid dreams • depression • disorientation or confusion • feeling anxious • hallucinations (seeing or hearing things that are not really there) • irritability	• memory problems • obsessive-compulsive symptoms • restlessness • sleepwalking • stuttering • suicidal thoughts and actions • tremor or shakiness • trouble sleeping • uncontrolled muscle movements

You should take montelukast for allergic rhinitis or hay fever only if you cannot tolerate other medicines or they do not work for you. Many other safe and effective allergy medicines are widely available, including over-the-counter medicines without a prescription. These include antihistamines such as loratadine (Alavert, Claritin), fexofenadine (Allegra), cetirizine (Zyrtec), levocetirizine (Xyzal), and diphenhydramine (Benadryl), as well as steroid nasal sprays such as fluticasone (Flonase), triamcinolone (Nasacort), and budesonide (Rhinocort). Alternatively, allergy shots have been shown to decrease symptoms of allergic rhinitis. Talk to your pharmacist or health care professional for help deciding which might be best.

What should health care professionals do?

Health care professionals should consider the risks and benefits of montelukast when deciding to prescribe or continue patients on the medicine. Counsel all patients receiving montelukast about mental health side effects, and advise them to stop the medicine and contact a health care professional immediately if they develop any symptoms included but not limited to those listed in the table above. Be aware that some patients have reported neuropsychiatric events after discontinuation of montelukast.

Only prescribe montelukast for allergic rhinitis in patients who have an inadequate response or intolerance to alternative therapies.

What did FDA find?
We reviewed case reports submitted to FDA*, conducted an observational study using data from the FDA's Sentinel System, and reviewed observational and animal studies in the published literature. Given the available information, we also reevaluated the benefits and risks of use of montelukast.

We continue to receive reports of mental health side effects reported with montelukast use. Consistent with our prior evaluations, a wide variety of mental health side effects have been reported, including completed suicides. Some occurred during montelukast treatment and resolved after stopping the medicine. Other reports indicated that mental health side effects developed or continued after stopping montelukast. The Sentinel study, which studied asthma patients 6 years and older, and other observational studies did not find an increased risk of mental health side effects with montelukast compared to inhaled corticosteroids (ICS). However, the Sentinel study and the observational studies had some limitations which may affect how we interpret the results. We also reviewed animal studies, which showed that montelukast given orally reaches the brain in rats.[1] (See Data Summary for more information)

Although new data regarding the risk of mental health side effects with montelukast are limited, we decided to strengthen the warnings by requiring a *Boxed Warning*. Due to the wide availability of alternative safe and effective allergy medicines with long histories of safety, we have reevaluated the risks and benefits of montelukast and have determined it should not be the first choice treatment particularly when allergic rhinitis symptoms are mild. In addition, many health care professionals and patients/caregivers are not aware of the risk of mental health side effects despite the existing warnings in the prescribing information.

We previously communicated about mental health side effects with montelukast in March 2008, January 2009, June 2009, and August 2009.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS) database.

What is my risk?
All medicines have side effects even when used correctly as prescribed. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking montelukast.

How do I report side effects from montelukast?
To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving montelukast or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Montelukast

- Montelukast is FDA-approved for asthma and allergies. It is a prescription medicine approved to prevent asthma attacks and for the long-term treatment of asthma in adults and children 1 year and older. It is approved to prevent exercise-induced asthma in patients 6 years and older. Montelukast is also approved to control the symptoms of allergic rhinitis, also known as hay fever, such as sneezing, stuffy nose, runny nose, and itching of the nose. It is used to treat seasonal outdoor allergies in patients 2 years and older, and year-round indoor allergies in patients 6 months and older.
- Montelukast blocks substances in the body called leukotrienes to help improve symptoms of asthma and allergic rhinitis.
- Montelukast is marketed under the brand name Singulair and as generics. It is available as tablets, chewable tablets, and oral granules.
- Common side effects of montelukast include upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhea, earache or ear infection, flu, runny nose, and sinus infection.
- In 2018, approximately 9.3 million patients of any age received a dispensed prescription for montelukast from U.S. outpatient retail pharmacies. Of these, approximately 2.3 million were children younger than 17 years.[2]

Additional Information for Patients and Parents/Caregivers

- FDA is requiring a *Boxed Warning* stating that serious mental health side effects that may include suicidal thoughts or actions have been reported in patients taking the asthma and allergy medicine montelukast (Singulair).
- Most reported cases occurred during montelukast treatment, but some occurred after stopping the medicine. In many cases, symptoms resolved after stopping montelukast; however, in some cases symptoms continued after stopping.
- Serious mental health side effects have occurred in patients with and without a history of mental illness.
- Talk with your health care professional about the benefits and risks of montelukast, as many other safe and effective allergy medicines are widely available, including over-the-counter ones, without a prescription. These include antihistamines such as loratadine (Alavert, Claritin), fexofenadine (Allegra), cetirizine (Zyrtec), levocetirizine (Xyzal), and diphenhydramine (Benadryl), as well as steroid nasal sprays such as fluticasone (Flonase), triamcinolone (Nasacort), and budesonide (Rhinocort). Alternatively, allergen immunotherapy, also known as allergy shots, has been shown to decrease symptoms of allergic rhinitis. A pharmacist or other health care professional can help you decide which might be best.
- Stop taking montelukast and notify a health care professional right away if you or your child experience behavior or mood-related changes while taking the medicine. These may include:

• agitation, including aggressive behavior or hostility • attention problems • bad or vivid dreams • depression • disorientation or confusion • feeling anxious • hallucinations (seeing or hearing things that are not really there) • irritability	• memory problems • obsessive-compulsive symptoms • restlessness • sleepwalking • stuttering • suicidal thoughts and actions • tremor or shakiness • trouble sleeping • uncontrolled muscle movements

- Talk to your health care professional about any history of mental illness before starting treatment.
- If you have allergies, there are a number of steps you can take to lessen your symptoms. These include avoiding exposure to allergy triggers, keeping indoor air clean, and taking allergy medicines. For more information, please see Allergy Relief for Your Child.
- We are requiring a new patient Medication Guide, which you should read every time you receive a prescription for montelukast. The Medication Guide explains the mental health risks and other important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Talk to your health care professional if you have any questions or concerns.
- To help FDA track safety issues with medicines, report side effects from montelukast or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is requiring a *Boxed Warning* stating that serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in patients taking montelukast (Singulair).
- We are recommending that montelukast should only be used for allergic rhinitis in patients who have an inadequate response or intolerance to alternative therapies.
- Ask patients about any history of psychiatric illness prior to initiating treatment.
- Consider the risks and benefits of montelukast when deciding to prescribe or continue patients on the medicine.
- Advise all patients of the risk of neuropsychiatric events when prescribing montelukast. Warnings about these side effects are included in the existing prescribing information; however, many health care professionals and patients/caregivers are not aware of this risk, and suicides and other adverse events continue to be reported.
- Advise patients and parents/caregivers that the patient should stop taking montelukast and contact a health care professional immediately if changes in behavior or new neuropsychiatric symptoms, suicidal thoughts or behavior occur.
- Monitor all patients treated with montelukast for neuropsychiatric symptoms. Events have occurred in patients with and without pre-existing psychiatric disease.

- Most reported cases of neuropsychiatric events occurred during montelukast treatment, but some occurred after discontinuation. In many cases, symptoms resolved after stopping montelukast; however, in some cases symptoms persisted after discontinuation from therapy or were reported after discontinuation of therapy.
- Encourage patients and parents/caregivers to read the Medication Guide they receive with their montelukast prescriptions, which explains the safety risks and provides other important information.
- To help FDA track safety issues with medicines, report adverse events involving montelukast or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

We reviewed case reports submitted to FDA, conducted an observational study using data from FDA's Sentinel System, and reviewed observational and animal studies in the published literature.

We evaluated reporting trends for all neuropsychiatric adverse events associated with montelukast use reported in the FDA Adverse Event Reporting System (FAERS) database from the date of FDA approval in February 1998 through May 2019. There was an increase in reporting of neuropsychiatric events around the time of the initial communications from FDA in 2008. Other increases in reporting were due to duplicate reports or foreign reports. Despite outside influences on reporting patterns, we continue to receive reports of serious neuropsychiatric events with montelukast.

We also performed a focused evaluation of completed suicides. Our analysis included only reports submitted to FDA, so there may be additional cases about which we are unaware. We identified 82 cases of completed suicide associated with montelukast, with many reporting the development of concomitant neuropsychiatric symptoms prior to the event. Forty-five cases were reported in patients older than 17 years, 19 cases were reported in those 17 years and younger, and 18 cases did not provide the age of the patient. The majority of the cases were reported by a family member or on social media. Most cases (48/82) did not contain sufficient information to evaluate the relationship between montelukast and the adverse events. The cases did not include key information such as the time to onset of the event, the use of concomitant medications, the presence of past or current comorbidities, including psychiatric illness; the degree of asthma control; and the presence of other risk factors for the events. Of the remaining 34 cases that were better documented, many contained additional risk factors that may have contributed to the suicide such as the use of medications or presence of comorbidities associated with increased risk for self-harm or behavioral disturbances. Six cases specifically reported concerns about not receiving education from a health care professional regarding the potential for neuropsychiatric side effects.

Using data from the FDA's Sentinel System from January 1, 2010, to September 30, 2015, we investigated if there is an increased risk of hospitalized and treated outpatient depressive disorders, self-harm, and suicides associated with montelukast use for asthma

compared to inhaled corticosteroids (ICS). We also evaluated if the risk of neuropsychiatric adverse events with montelukast compared to ICS was modified by the 2008 FDA Early Communication and changes to the montelukast prescribing information, or was affected by age, sex, and/or psychiatric history. Patients (n=457,377) 6 years and older diagnosed with asthma and exposed to montelukast or ICS were matched 1:1 on propensity scores. The risk of inpatient depressive disorder associated with montelukast use compared to ICS was not significant (overall HR: 1.06; 95% CI: 0.90-1.24). There were no significant risks among males, females, patients 12 years and older, patients with a psychiatric history, or after the 2008 FDA communication and prescribing information changes. Exposure to montelukast was also not associated with self-harm (HR:0.92; 95% CI: 0.69-1.21) or modified self-harm (HR: 0.81; 95% CI: 0.63-1.05). Four suicides occurred (two exposed to montelukast, two exposed to ICS), all in patients older than 18 years with a psychiatric history. Exposure to montelukast was significantly associated with a decreased risk of treated outpatient depressive disorder (overall hazard ratio [HR]: 0.91; 95% confidence interval [CI]: 0.89-0.93). Decreased risks were seen among patients with a history of a psychiatric disorder, in patients 12 to 17 years as well as 18 years and older, and in both females and males.

The Sentinel study had limitations. The study relied on outcomes for which patients sought medical attention that were recorded in health care claims. Thus, it was unable to evaluate either the entire spectrum of neuropsychiatric events or events that did not result in a billed encounter. Some neuropsychiatric events may have been handled by discontinuation of the drug without a health care encounter. Most of the usage occurred after the 2008 FDA communication and prescribing information changes about the risk of neuropsychiatric events, so montelukast patients may have been informed to cease treatment should depressive symptoms develop, resulting in a decreased risk among montelukast users. Lastly, the study was unable to adjust for socioeconomic status. However, a literature review did not reveal evidence that montelukast and ICS are prescribed disproportionally to patients of varying socioeconomic status. Patients with higher socioeconomic status may be more likely to seek asthma management through outpatient visits, resulting in increased surveillance for neuropsychiatric adverse events.

We also reviewed evidence from animal studies, which suggest montelukast could act directly on cells in the brain. Orally administered montelukast (10 mg/kg/day for 7 days) was detectable in brain tissue and cerebrospinal fluid in rats, providing evidence of its ability to cross the blood-brain barrier.[1]

References

1. Marschallinger J, Schäffner I, Klein B, Gelfert R, Rivera FJ, Illes S, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun 2015;6:8466.

2. IQVIA Total Patient Tracker™. Year 2018. Data extracted June 2019.

Related Information

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The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

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FDA NEWS RELEASE

FDA Requires Stronger Warning About Risk of Neuropsychiatric Events Associated with Asthma and Allergy Medication Singulair and Generic Montelukast

For Immediate Release:

March 04, 2020

Español (/news-events/press-announcements/la-fda-requiere-una-advertencia-mas-fuerte-sobre-los-riesgos-de-eventos-neuropsiquiatricos-asociados)

The U.S. Food and Drug Administration today announced that it is requiring a boxed warning – the agency's most prominent warning – for montelukast (sold under the brand name Singulair and in generic form) to strengthen an existing warning about the risk of neuropsychiatric events associated with the drug, which is used to treat asthma and allergic rhinitis (hay fever). The boxed warning advises health care providers to avoid prescribing montelukast for patients with mild symptoms, particularly those with allergic rhinitis.

As noted in a new Drug Safety Communication (/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug) issued today, the warning follows the FDA's review of available data regarding continued reports of neuropsychiatric events with montelukast, such as agitation, depression, sleeping problems, and suicidal thoughts and actions. The Drug Safety Communication includes recommendations for health care professionals and patients and a summary of the data that led to these warnings.

"We recognize that millions of Americans suffer from asthma or allergies and rely on medication to treat these conditions. The incidence of neuropsychiatric events associated with montelukast is unknown, but some reports are serious, and many patients and health care professionals are not fully aware of these risks," said Sally Seymour, M.D., director of the Division of Pulmonary, Allergy and Rheumatology Products in the FDA's Center for Drug Evaluation and Research. "With today's action, the FDA aims to make sure patients and medical providers have the information available to make informed treatment decisions. Importantly, there are many other safe and effective medications to treat allergies with extensive history of use and safety, such that many products are available over the counter without a prescription."

The FDA updated the product labeling in 2008 to include information about neuropsychiatric events reported with use of montelukast. In response to continued reports of suicide and other adverse events, the FDA evaluated available data regarding the risk of neuropsychiatric events, including reports submitted through the FDA Adverse Event Reporting System (FAERS) (/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard) and observational studies in the published literature. The FDA also conducted an observational study using data in the Sentinel Distributed Database (https://www.sentinelinitiative.org/drugs/assessments/neuropsychiatric-events-following-montelukast-use-propensity-score-matched) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) and presented the findings at an FDA advisory committee meeting in 2019.

As part of its review, the FDA re-evaluated the benefits and risks of montelukast as the treatment landscape has evolved since the drug was first approved in 1998. Based upon this assessment, the FDA determined the risks of montelukast may outweigh the benefits in some patients, particularly when the symptoms of the disease are mild and can be adequately treated with alternative therapies. For allergic rhinitis in particular, the FDA has determined that montelukast should be reserved for patients who have not responded adequately to other therapies — or who cannot tolerate these therapies.

In addition to the boxed warning, the FDA is also requiring a new Medication Guide to be given to patients with each montelukast prescription.

Health care professionals and patients should report side effects from montelukast to the FDA's MedWatch program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda).

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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