# Food and Drug Administration (FDA) Update Singulair (montelukast) Boxed Warning

## Updated warning and precautions for use of Montelukast

In 2020, the FDA updated the warning and precautions for montelukast to include a new Boxed Warning following post-marketing observations. Montelukast was first approved by the FDA in 1998 under the brand name Singulair.[1] Montelukast blocks leukotrienes that cause symptoms associated with asthma and allergic rhinitis, including sneezing, mucus secretion, and congestion. Common side effects include upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhea, earache or ear infection, flu, runny nose, and sinus infection.[2]

In post-marketing reports the use of montelukast has been linked to neuropsychiatric events that include agitation, aggressive behavior, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, stuttering, hallucinations, insomnia, irritability, memory impairment, obsessive compulsive symptoms, restlessness, sleep walking, suicidal thoughts and behaviors (including suicide), tic, and tremor.[2] The risk of neuropsychiatric events was previously noted in montelukast prescribing information as a precaution, but upon evaluation, the FDA determined that many healthcare providers and patients were not aware of the risk. In an FDA safety drug communication on March 4, 2020, the FDA required the addition of a Boxed Warning to all montelukast products stating that serious neuropsychiatric events, including suicidal thoughts, have been reported in patients taking montelukast.[1] The FDA stated:

**"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."[1]**

## FDA Review Findings

The FDA collected data from February 1998 through May 2019 through the FDA Adverse Event Reporting System (FAERS) database. The FDA, "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."[1]

### Prescribing Considerations

An FDA Boxed Warning is the most stringent warning required by the FDA. In addition to updating prescribing information, the FDA is also requiring a new patient medication guide to advise patients of the risk of neuropsychiatric events. When prescribing montelukast the benefits of use should be weighed against the risk of neuropsychiatric events. Patients and caregivers should be aware of the risk and be alert to behavioral changes. If behavioral changes occur, patients should be advised to contact a healthcare provider. Discontinue therapy if neuropsychiatric symptoms occur and continue to monitor behavior. Behavioral changes dissipate in most cases after discontinuation of montelukast. There is insufficient data to determine if a patient is at high-risk for neuropsychiatric symptoms; therefore, during treatment with montelukast, patients should be monitored closely for behavioral changes and re-evaluated for the necessity of treatment with montelukast.[1,2] To help you evaluate your patients and for possible alternative treatment options, please see below:

FDA-approved indications for montelukast[2]

**Maintenance treatment of asthma in patients 12 months of age and older**
Examples of alternative treatment options include inhaled corticosteroids (i.e., fluticasone, budesonide, beclomethasone) and combination inhalers (i.e., fluticasone-salmeterol, budesonide-formoterol)[3]

**Acute prevention of exercise-induced bronchoconstriction in patients 6 years of age and older**
Examples of alternative treatment options include short-acting beta agonists (i.e., albuterol) and mast cell stabilizers (i.e., cromolyn)[4]

**Relief of symptoms of allergic rhinitis**
Examples of alternative treatment options include oral antihistamines (i.e., cetirizine, loratadine), intranasal corticosteroids (i.e., fluticasone), intranasal antihistamines (i.e., azelastine, olopatadine), combination intranasal corticosteroid and antihistamine (i.e., azelastine/fluticasone), oral decongestants (i.e., pseudoephedrine), intranasal mast cell stabilizers (i.e., cromolyn), and intranasal anticholinergics (i.e., ipratropium)[5]

**Seasonal allergic rhinitis in patients 2 years of age and older**
Examples of alternative treatment options include oral antihistamines (i.e., cetirizine, loratadine), intranasal corticosteroids (i.e., fluticasone), intranasal antihistamines (i.e., azelastine, olopatadine), and intranasal mast cell stabilizers (i.e., cromolyn)[6]

**Perennial allergic rhinitis in patients 6 months of age and older**
Examples of alternative treatment options include oral antihistamines (i.e., cetirizine), intranasal corticosteroids (i.e., fluticasone), and intranasal antihistamines (i.e., azelastine)[5]

## Goal of the Drug Utilization Review Team

The UnitedHealthcare Community Plan drug utilization review program is administered to promote the safe and efficacious use of medications. These interventions do not take into consideration patient-specific variables. The intent of this newsletter is to bring attention to potential medication related issues. UnitedHealthcare Community Plan is committed to continuing to provide the best possible care for our members.



[1]FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. Food and Drug Administration Web Site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug. Accessed November 11, 2020.
[2]Singluair [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2020.
[3]Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed February 2, 2020.
[4]Parsons J, Hallstrand T, Mastronarde J, Kaminsky D, Rundell K, Hull J, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016–1027.
[5]Sur D, Plesa M. Treatment of Allergic Rhinitis. Am Fam Physician. 2015;92(11):985-992.
[6]Emeryk A, Emeryk-Maksymiuk J, Janeczek K. New guidelines for the treatment of seasonal allergic rhinitis. Postepy Dermatol Alergol. 2019;36(3):255–260.


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