

衛生署藥物辦公室
藥物資訊及警戒科
香港九龍觀塘巧明街 100 號
Landmark East 友邦九龍大樓
20 樓 2002-05 室



DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG INFORMATION AND
PHARMACOVIGILANCE DIVISION
Suites 2002-05, 20/F, AIA Kowloon Tower
Landmark East, 100 How Ming Street
Kwun Tong, Kowloon, Hong Kong

電話號碼 Tel. No.: 3974 4175 (852)
詢問處 Enquiries (852) 3974 4175
傳真號碼 Faxline No.: (852) 2803 4962
本署檔號 OUR REF.:

DH DO PRIE/7-30/15
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5 Mar 2020

Dear Healthcare Professionals,

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

Your attention is drawn to the US Food and Drug Administration's (FDA) announcement that it 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.

FDA is taking this action after a review of available information led it 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. FDA 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, FDA has determined that montelukast should be reserved for those who are not treated effectively with or cannot tolerate other allergy medicines. For patients with asthma, FDA recommends that health care professionals consider the benefits and risks of mental health side effects before prescribing montelukast.

Patients and parents/caregivers should stop montelukast and discuss with a health care professional right away if they or their 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. They should take montelukast for allergic rhinitis or hay fever only if they cannot tolerate other medicines or they do not work for them. Many other safe and effective allergy medicines are widely available. Talk to their pharmacist or health care professional for help deciding which might be best.

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 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.

FDA 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, FDA also reevaluated the benefits and risks of use of montelukast. FDA continues to receive reports of mental health side effects reported with montelukast use. Consistent with its 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. However, the Sentinel study and the observational studies had some limitations which may affect how FDA interpret the results. FDA also reviewed animal studies, which showed that montelukast given orally reaches the brain in rats.

Although new data regarding the risk of mental health side effects with montelukast are limited, FDA 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, FDA has reevaluated the risks and benefits of montelukast and has 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.

Please refer to the following website in FDA for details:

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug>

In Hong Kong, there are 52 registered pharmaceutical products containing montelukast, and all products are prescription-only medicines. So far, the Department of Health (DH) has received 3 cases of adverse drug reaction related to montelukast, of which one case is related to neuropsychiatric events.

Related news was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 15 Jun 2009, with the latest update posted on 20 Sep 2019. Letters to remind local healthcare professionals were issued by the DH on 20 Sep 2019. In Feb 2020, the Registration Committee of the Pharmacy and Poisons Board discussed the risk of neuropsychiatric reactions of montelukast, including speech impairment and obsessive-compulsive symptoms, and decided to remain vigilant on any related safety updates by other overseas drug regulatory authorities on this issue. In light of the above FDA's announcement, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Undesirable Medical Advertisements and Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": <http://www.drugoffice.gov.hk/adr.html>. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,



(Joseph LEE)

for Assistant Director (Drug)