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DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION
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20 Sep 2019

Dear Healthcare Professionals,

Montelukast (Singulair): reminder of the risk of neuropsychiatric reactions

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) alert for neuropsychiatric reactions in patients taking montelukast. Prescribers should carefully consider the benefits and risks of continuing treatment if neuropsychiatric reactions occur.

It has been known for some time that neuropsychiatric reactions may occur in association with montelukast treatment, and these reactions are listed as possible side effects in the product information in the UK. A recent EU review confirmed the known risks of neuropsychiatric reactions and found that the magnitude of risk was unchanged. However, the review identified some cases in which there had been a delay in neuropsychiatric reactions being recognised as a possible adverse drug reaction.

A range of neuropsychiatric reactions has been reported in association with montelukast. Among these are: sleep disturbances, depression and agitation (may affect up to 1 in 100 people taking montelukast); disturbances of attention or memory (up to 1 in 1,000 people); and very rarely, hallucinations and suicidal behaviour (up to 1 in 10,000 people).

In the UK, between 2014 and 2018, MHRA received 219 reports of suspected adverse neuropsychiatric reactions to the Yellow Card Scheme, during which time there were approximately 14 million prescriptions of montelukast. Since montelukast was first marketed in the UK, MHRA has received 639 reports of suspected adverse neuropsychiatric reactions. In the UK, the most frequently reported suspected neuropsychiatric reactions associated with montelukast have been nightmares/night terrors, depression, insomnia, aggression, anxiety and abnormal behaviour or changes in behaviour. These events were reported in all age groups. However, nightmare/night terrors, aggression, and behaviour changes are more frequently reported in the paediatric population.

The EU review also evaluated very rare reports of cases of speech impairment (dysphemia), described as 'stuttering'. Most of the cases were reported in children younger than 5 years, occurred shortly after montelukast was started (median time to onset 8 days) and sometimes occurred in conjunction with other suspected neuropsychiatric events. Where information was provided, in most cases the events resolved on stopping treatment

In addition, the EU review endorsed the inclusion in the product information of very rare reports of obsessive–compulsive symptoms in the product information. Cases of obsessive-compulsive symptoms were reported to generally occur after a longer treatment period (median time to onset of 61 days) and sometimes occurred in conjunction with other neuropsychiatric events. Where information was provided, in most cases the events resolved on stopping treatment.

Healthcare professionals are advised:

- Be alert for neuropsychiatric reactions in patients taking montelukast; events have been reported in adults, adolescents, and children.
- Advise patients and their caregivers to read carefully the list of neuropsychiatric reactions in the patient information leaflet and seek medical advice immediately should they occur.
- Evaluate carefully the risks and benefits of continuing treatment if neuropsychiatric reactions occur.
- Be aware of newly recognised neuropsychiatric reactions of speech impairment (stuttering) and obsessive–compulsive symptoms.

Patients and caregivers are advised:

- It is important that the patient or his/her child does not stop montelukast without talking to a doctor or asthma nurse first.
- Adverse reactions affecting sleep, behaviour, and mood have been infrequently reported in people taking montelukast.
- Always read the leaflet that accompanies their or their child's medicines, and talk to a healthcare professional if they suspect any serious reactions to montelukast.

Please refer to the following website in MHRA for details:

https://www.gov.uk/drug-safety-update/montelukast-singulair-reminder-of-the-risk-of-neuropsychiatric-reactions

In Hong Kong, there are 52 registered pharmaceutical products containing montelukast and 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 was related to neuropsychiatric reactions, including speech disorder (strange speech). Related news was previously issued by United States Food and Drug Administration, Australia Therapeutic Goods Administration, Taiwan Food and Drug Administration, and was posted on the Drug Office website on 15 Jun 2009, 13 Jul 2018 and 28 Jul 2018 respectively. Neuropsychiatric adverse effects of montelukast are documented in reputable drug references such as Martindale: The Complete Drug Reference. In light of the newly recognized neuropsychiatric reactions of speech impairment and obsessive-compulsive symptoms in the above MHRA's announcement, the matter will be 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 Pharmacovigilance 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)