DRUG SAFETY INFORMATION **No.71**

30 October 2020

Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way #11-03 Helios
Singapore 138667
Website: www.hsa.gov.sg
Fax: 6478 9069

Dear Healthcare Professional

ADVISORY ON RESTRICTION ON THE USE OF MONTELUKAST AND NEUROPSYCHIATRIC EFFECTS

The Health Sciences Authority (HSA), in consultation with its Product Vigilance Advisory Committee (PVAC), would like to inform healthcare professionals of the new restriction on the use of montelukast due to the risk of neuropsychiatric events. This follows HSA's benefit-risk assessment of montelukast which concluded that the benefits of montelukast for use in allergic rhinitis patients remain favourable if additional precautionary measures are put in place to mitigate the known but rare risk of neuropsychiatric events. These measures include restricting the use of montelukast in the treatment of allergic rhinitis to patients who have inadequate response or are intolerant to alternative therapies, and the strengthening of existing warnings on neuropsychiatric risks in the package inserts (PIs) of montelukast-containing products. Healthcare professionals are advised to consider the benefits of treatment and risks of neuropsychiatric effects before prescribing montelukast.

Background

2 Montelukast is a selective leukotriene receptor antagonist (LTRA) that has been registered in Singapore since 1998 for the prophylaxis and chronic treatment of asthma and the relief of symptoms of allergic rhinitis. Locally, there are 32 registered products that contain montelukast (Annex A). Warnings on the risk of neuropsychiatric events (e.g. sleep disturbances, agitation) associated with montelukast are already stated in the PIs of locally registered montelukast products.

3 In March 2020, HSA initiated a safety review on montelukast in response to the regulatory actions taken by the US Food and Drug Administration (FDA)[1] to include a Boxed Warning on serious behaviour and mood-related changes with montelukast and to restrict the use of montelukast in the treatment of allergic rhinitis in patients with inadequate response or intolerance to alternative therapies. FDA's review did not identify new evidence regarding the known neuropsychiatric safety concern but highlighted a lack of awareness of healthcare professionals to this safety issue despite earlier communications by the agency.

4 Internationally, several regulatory agencies had also incorporated restrictions to the use of montelukast in allergic rhinitis. In July 2020, Health Canada adopted similar measures as the US FDA.[2] In the United Kingdom, montelukast is only indicated for symptomatic relief of seasonal allergic rhinitis in patients with asthma.

International clinical practice guidelines on the use of montelukast [3,4,5]

5 International clinical practice guidelines on the treatment of allergic rhinitis recommend the use of intranasal steroid (e.g. mometasone, fluticasone) and/or oral antihistamines (e.g. cetirizine, loratadine) as primary therapies for allergic rhinitis. In particular, the American Academy of Otolaryngology-Head and Neck Surgery Foundation recommended against the use of LTRAs, including montelukast, as primary treatment therapy for allergic rhinitis, except in asthmatic patients. The British Society of Allergy and Clinical Immunology also recommended that LTRAs may have a place in therapy for asthmatic patients with seasonal allergic rhinitis. The Global Initiative for Asthma (GINA) guideline lists montelukast as an option for initial controller therapy in asthma.

Local reports of neuropsychiatric AEs associated with montelukast

6 To date, HSA has received several reports of neuropsychiatric events associated with the use of montelukast since its registration in Singapore in 1998. The events include aggressive behaviour, agitation, depression, tremor, hallucinations, hyperactivity, and sleep disturbances such as somnolence, insomnia and nightmares. Most of these events were non-serious and none included suicidal behaviour. The use of concomitant medicines and/or presence of comorbidities were not reported for most cases, limiting firm causality assessment.

HSA's benefit-risk assessment

7 HSA's benefit-risk assessment took into consideration the local safety data, current international clinical practice guidelines on the treatment of allergic rhinitis and asthma, the availability of alternative treatments for allergic rhinitis, inputs from local clinicians (including respiratory specialists, general practitioners and psychiatrists) and international regulatory actions.

8 Based on currently available information, HSA, in consultation with its PVAC, concluded that the benefit-risk profile of montelukast remains favourable for its approved indications, if additional precautionary measures are taken to mitigate the risk of neuropsychiatric events. These additional measures include restricting the use in allergic rhinitis to patients who are inadequately treated or intolerant to alternative therapies and the strengthening of warnings on neuropsychiatric events in the PIs of products containing montelukast.

HSA's advisory and actions

9 Healthcare professionals are advised of the following:

- To consider the benefits of treatment with montelukast and its risks of neuropsychiatric effects before prescribing montelukast
- To discuss with their patients and/or caregivers on the benefits and risks of treatment when prescribing montelukast. Healthcare professionals may make use of the patient educational material available for montelukast (e.g. article on MOH Health Hub) for patient counselling
- To advise their patients and/or caregivers to be alert to changes in behaviour or new neuropsychiatric symptoms when taking montelukast and to seek medical attention if neuropsychiatric symptoms occur

10 HSA is working with the product registrants to update the local PIs of montelukast-containing products with the new recommendations on the indicated use of montelukast in allergic rhinitis and additional safety information on the risk of neuropsychiatric AEs.

11 Healthcare professionals are encouraged to report any suspected serious adverse reactions related to use of products containing montelukast to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 6478 9069, or report online at http://www.hsa.gov.sg/adverse-events. Should you have further queries regarding this matter, please contact Ms Liesbet Tan at Tel: 6304 5464 or email: liesbet_tan@hsa.gov.sg.

Thank you.

Yours faithfully

MS JALENE POH
DIRECTOR
VIGILANCE AND COMPLIANCE BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health

Annex 1

List of Registered Montelukast-containing Products

S/No	Product Name	Registrant
1	Actamone Chewable Tablet 4mg	Drug Houses Of Australia Pte. Ltd.
2	Actamone Chewable Tablet 5mg	Drug Houses Of Australia Pte. Ltd.
3	Actamone F.C. Tablet 10mg	Drug Houses Of Australia Pte. Ltd.
4	Apo-Montelukast Film Coated Tablet 10mg	Pharmaforte Singapore Pte Ltd
5	Klairmont Film-Coated Tablet 10mg	Pharmakoe Pte. Ltd.
6	Lukakline Chewable Tablet 4mg	Zyfas Medical Co
7	Lukakline Chewable Tablet 5mg	Zyfas Medical Co
8	Lukakline Tablet 10mg	Zyfas Medical Co
9	Monast 10 Montelukast Sodium Tablets 10mg	Medicell Pharmaceutical (S) Pte. Ltd.
10	Monast 4 Montelukast Sodium Paediatric Chewable Tablet 4mg	Medicell Pharmaceutical (S) Pte. Ltd.
11	Montek Chewable Tablets 4mg	Ranbaxy (Malaysia) Sdn. Bhd.
12	Montek Chewable Tablets 5mg	Ranbaxy (Malaysia) Sdn. Bhd.
13	Montelair Chewable Tablet 5mg	Goldplus Universal Pte Ltd
14	Montelair Tablet 10mg	Goldplus Universal Pte Ltd
15	Montelukast Sandoz Film Coated Tablet 10mg	Novartis (Singapore) Pte Ltd
16	Montelukast Sandoz Oral Granules 4mg/Sachet	Novartis (Singapore) Pte Ltd
17	Montelukast Mevon Chewable Tablets 4mg	Novem Pharma Pte Ltd
18	Montelukast Mevon Chewable Tablets 5mg	Novem Pharma Pte Ltd
19	Montelukast Mevon Film-Coated Tablets 10mg	Novem Pharma Pte Ltd
20	Montelukast Sandoz Chewable Tablets 4mg	Novartis (Singapore) Pte Ltd
21	Montelukast Sandoz Chewable Tablets 5mg	Novartis (Singapore) Pte Ltd
22	Oxair Film Coated Tablet 10mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
23	PMS-Montelukast Chewable Tablets 4 Mg	Medicell Pharmaceutical (S) Pte. Ltd.
24	PMS-Montelukast Chewable Tablets 5mg	Medicell Pharmaceutical (S) Pte. Ltd.
25	PMS-Montelukast Fc Tablets 10mg	Medicell Pharmaceutical (S) Pte. Ltd.
26	Regulair Chewable Tablet 4mg	Pan-Malayan Pharmaceuticals Pte Ltd
27	Regulair Chewable Tablet 5mg	Pan-Malayan Pharmaceuticals Pte Ltd
28	Regulair Tablet 10mg	Pan-Malayan Pharmaceuticals Pte Ltd
29	Singulair Chewable Tablet 4mg	MSD Pharma (Singapore) Pte. Ltd.
30	Singulair Chewable Tablet 5mg	MSD Pharma (Singapore) Pte. Ltd.
31	Singulair Oral Granules 4mg/Sachet	MSD Pharma (Singapore) Pte. Ltd.
32	Singulair Tablet 10mg	MSD Pharma (Singapore) Pte. Ltd.

References

1. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug
2. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/august-2020.html
3. Otolaryngol Head Neck Surg 2015, 152(1S): S1-43
4. Clin Exp Allergy. 2017;47: 856–889.
5. www.ginasthma.org