Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement 8, Thursday 5 and Friday 6 April 2018

Section A: Submissions for registration

The committee's advice was sought on nine new pre-market applications for prescription medicines, and one risk management plan for a generic prescription medicine. The applications (table below) included new entities, new fixed combination, extension of indications, and new directions for use, and a generic medicine.

Number of applications	Application Type	Main consideration by ACM (among other items)
4	Type A - New Chemical /Biological Entity/Biosimilar	For general consideration
1	Type B – New Fixed Combination	For general consideration
3	Type C - Extension of Indications	For consideration of broader indication without substantiating supportive evidence.
1	Type F – Major Variation (New Strength)	For general consideration
1	Type D – Generic Medicine	For consideration relating to the Risk Management Plan

Further details of the ACM discussions and advice associated with pre-market items are released within the Australian Public Assessment Reports (AusPARs) for each new active. Please note that there is a delay from when an application was considered at ACM and the publication of the AusPAR. To browse all AusPARs see: <https://www.tga.gov.au/browse-auspars-active-ingredient>

Section B: Post-Market items referred for advice

Two items were referred to the committee for its advice.

1. Montelukast and neuropsychiatric adverse events

The ACM was asked to provide advice on the safety of montelukast regarding neuropsychiatric adverse events, following media interest in this issue.

Montelukast was approved for use in Australia in 1998 and is available under several brand names. The approved indications are prophylaxis and treatment of chronic asthma in adults and children 2 years of age or older, and symptomatic treatment of seasonal allergic rhinitis.

Neuropsychiatric events can include agitation, aggressive behaviour or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism [sleep-walking], suicidal thinking and behaviour, and tremor. Neuropsychiatric events have been reported in adult, adolescent, and paediatric patients taking montelukast.

The ACM noted that in order to build a composite picture of the overall safety profile of a particular medicine, evidence from a number of different sources and types of studies needs to be collated. The current evidence regarding an association between montelukast and neuropsychiatric events is conflicting.

Review of evidence

Members noted the literature review conducted by the TGA identified two retrospective cohort studies (Ali et al[1], Benard et al[2]), two pharmacovigilance studies (Haarman et al[3], Aldea Perona et al[4]) and one systematic review (Law et al[5]) examining the possible association between neuropsychiatric symptoms and montelukast had been published between January 2013 and February 2018.

There was at least some evidence to support a causal association between montelukast and neuropsychiatric events, including: evidence from pharmacovigilance studies and observational studies; the consistency of the association across multiple countries and databases; and a positive de-challenge/re-challenge association in a small number of patients in some studies. However, to date there is no biologically plausible explanation to link the pharmacological actions of montelukast with the development of neuropsychiatric events.

The ACM noted the following points that may have contributed to the discordancy between cohort studies and pharmacovigilance findings:

· The conglomeration of symptoms and diagnoses under the 'neuropsychiatric' term does not assist in the assessment of incidence of critical events. The wide array of

[1] Ali MM, O'Brien CE, Cleves MA, Martin BC. Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. Pharmacoepidemiol Drug Saf. 2015;24:434-444. DOI: 10.1002/pds.3758
[2] Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J. 2017;50. doi:10.1183/13993003.00148-2017
[3] Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. Pharmacol Res Perspect. 2017;5 e00341. doi: 10.1002/prp2.341
[4] Aldea Perona A, García-Sáiz M, Sanz Álvarez E. Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase®. Drug Safety 2016;39:69-78. DOI 10.1007/s40264-015-0360-2
[5] Law SWY, Wong AYS, Anand S, et al. Neuropsychiatric Events Associated with Leukotriene-Modifying Agents: A Systematic Review. Drug Saf 2018; 41:253-265. doi:10.1007/s40264-017-0607-1

symptoms reported were not necessarily formal psychiatric diagnoses (e.g. disturbed sleep). Isolation of serious neuropsychiatric toxicity from background risks in the populations of concern is difficult within the available data.

- The cohort studies may not have been powered sufficiently to detect rare outcomes.
- The likely influence of selection bias in clinical studies, and reporting and detection bias in the pharmacovigilance studies.
- There are factors that complicate analysis: a higher incidence of agitation observed in children by their parent/carer could be due to higher energy levels once the asthma is adequately treated; chronic disease such as asthma is associated with depression.

The ACM advised that while the evidence of association/causality between montelukast and neuropsychiatric events is not robust, the persistent signal requires vigilance due to the potential impact of serious adverse events, although those events have a low probability of occurring.

Risk minimisation

The ACM considered that in current clinical practice montelukast is a useful first line treatment for mild to moderate asthma (but not severe asthma) in a small but well-defined population. Advantages of montelukast compared to inhaled corticosteroids are ease of administration and a favourable overall safety profile.

The ACM commented favourably on the montelukast fact sheet on the Asthma Australia website.[6] The fact sheet provides advice about the small risk of children on montelukast becoming emotionally unstable, and recommends that prescribers should discuss this risk with parents/carers, and that parents/carers need to be alert to possible adverse effects. The ACM noted that equivalent information is not included across the range of clinical guidances that prescribers may use as primary reference sources.

The ACM advised that it would be helpful if the TGA liaised with the various authoring bodies of guidance documents and asthma management plan templates used by prescribers and asthma nurse educators, to insert advice similar to that in the Asthma Australia fact sheet. Given the early appearance of adverse events (within 14 days of initiation), active follow-up by prescribers with the patient in this timeframe would also be helpful.

The ACM highlighted that the assessment of the effectiveness of a risk minimisation activity, such as revised clinical guidance, needs to be considered in advance of its implementation.

The ACM noted that current risk minimisation measures in Australia are comparable to other jurisdictions.

The ACM did not propose changes to the Product Information (PI) or the Consumer Medicines Information (CMI). The committee did not recommend another TGA web statement. [See Medicines Safety Update, April 2013].

The ACM had no objection to the inclusion of the CMI in the packaging, while recognising that provision of printed material in this way is a passive activity and that the CMI may or may not be read and remembered by the patient, parent and/or carer.

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[6] https://www.asthmaaustralia.org.au/news/national/montelukast-latest-information (accessed 9 April 2018)

The ACM emphasised that the provision of information on medicines to consumers should not rely solely on the inclusion of the CMI in the packaging. Rather, the ACM advised and supported the active provision of the CMI to the parent or carer, with counselling, at the point of dispensing.

2. Patient alert cards

Patient alert card are generally wallet-sized cards that contain critical safety messages for patients and their healthcare providers. The cards are required for only a small number of medicines. The need for a patient alert card is determined as part of the evaluation of the risk minimisation activities within the Risk Management Plan.

The ACM provided advice on the purpose, content, format and supply of patient alert cards, as part of ongoing policy development by the TGA.

Further information

For further information on the ACM, please visit Advisory Committee on Medicines

or contact the ACM Secretary by email ACM@health.gov.au.