Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement

Meeting 14, Thursday 4 April 2019

Section A: Pre-market registration applications referred for advice

At this meeting, the committee's advice was sought on 6 applications under evaluation by the TGA. The applications included: four for the registration of a new chemical entity; one seeking extensions of indications and a new dosage form; and one seeking registration of a new dose form and strengths.

Further details of the ACM discussion and advice associated with these items are released within the Australian Public Assessment Reports (AusPARs). 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/ws-auspar-index>

Section B: Post-market items referred for advice

At this meeting, the committee's advice was sought on the following post-market items.

Bufexamac and allergic contact dermatitis

Bufexamac is a non-steroidal anti-inflammatory drug (NSAID). There are 13 medicines currently available in Australia that contain bufexamac 50 mg/g, in combination with chlorhexidine and lidocaine (lignocaine). The medicines are topical creams, approved for use in the treatment of minor cuts, abrasions, insect bites, stings and itches, and minor burns and sunburn.

The medicines are not scheduled (i.e. the medicines are available over-the-counter for general sale) and have been available for many years from various sponsors.

The ACM discussed the risk of potentially serious skin reactions in patients using bufexamac for the treatment of minor ailments. The committee noted the following points.

- The TGA has received 48 reports for bufexamac-containing products for any adverse event, including 7 cases that involved hospital admission.

- Australian case series by Pan et al and Harris et al have documented 6 cases of cutaneous eruptions with a temporal relationship to bufexamac use.
- An Australian 10-year retrospective study found 19/899 (2%) patients patch tested positively to bufexamac.
- Internationally, of 662 reports for bufexamac in the WHO global database of adverse events, nearly 10% of the reports were classified as serious.
- The European Commission revoked the market authorisations for bufexamac in 2010.

In a review undertaken in 2011 by the TGA, which resulted in changes to product labelling, factors that increased the risk of contact allergy to bufexamac were identified as: young age; atopic dermatitis; frequent/chronic exposure; eczematous and inflammatory skin conditions; and female gender.

The ACM noted the following issues relating to risk.

- There have been rare reports of serious skin reactions following use of bufexamac, including generalised acute contact dermatitis, erythema multiforme-like reactions and acute generalised exanthematous pustulosis; when severe, these conditions can lead to scarring, a need for skin grafts and permanent disability.
- Consumers may be unable to discriminate between the original skin condition and an allergic reaction to the cream and so application of the cream to the skin may continue.
- Consumers are unlikely to suspect harm from a readily available first aid product and adverse reactions to a first aid cream are likely to be significantly under-reported.
- The creams are contraindicated for persons with skin sensitivities at the same time as the cream is indicated for 'itches', which are typical for persons with atopic conditions.
- Medical literature on bufexamac is sparse, mostly dating from prior to cancellation of bufexamac-containing medicines in Europe.

The ACM was not aware of a pattern of similar adverse events to other topical NSAIDs available in Australia. The ACM noted that the safety issue was specific to bufexamac and that the other active ingredients in the formulations (chlorhexidine, lidocaine) were not implicated in this safety issue.

The ACM noted that changes to product labelling had been implemented since 2011 to alert consumers to the risk of local skin reactions and to advise against prolonged use and discourage use by atopic individuals. However, reports of serious skin reactions to bufexamac have been received by the TGA since these labelling changes.

The ACM advised that the removal of bufexamac-containing medicines from the Australian market would not result in an unmet clinical need.

Erythropoiesis stimulating agents (ESAs) and increased mortality in patients with cancer; ESAs and cardiovascular risk

ESAs are growth factors that primarily stimulate red blood cell production. ESAs may be short-acting (epoetin alfa, epoetin beta, epoetin lambda) or long-acting (darbepoetin alfa, methoxy polyethylene glycol-epoetin beta).

Some ESAs are indicated for the treatment of anaemia in patients with a nonmyeloid malignancy where anaemia develops as a result of concomitantly administered chemotherapy. All ESAs registered in Australia are indicated for use in the treatment of anaemia associated with chronic renal failure (CRF).

In 2008 Australian Product Information (PI) documents for ESAs were updated to reflect new data suggesting higher mortality rates in patients with cancer, and increased risk of cardiovascular and cerebrovascular events and other thromboembolic events when used in all patients, including CRF patients.

The ACM provided advice on current clinical practice in Australia with respect to the use of ESAs to treat anaemia in cancer patients, the situations where ESAs could be used outside of the approved therapeutic indications, and the guidelines used to support clinical decision making regarding the treatment of anaemia in cancer patients.

The ACM advised that there is sufficient evidence (i.e. multiple studies, meta-analyses and reviews) that shows decreased overall survival associated with the use of ESAs in patients with cancer.

The ACM advised that ESAs are effectively a second choice therapy for chemotherapy induced anaemia, used only where blood transfusion is not appropriate.

The ACM advised that the evidence is sufficient to justify additional risk mitigation for all ESAs indicated for cancer. They recommended consideration of a boxed warning being included in the PI, as the risk appears to be a class effect across all the agents and the risk does not appear related to whether the ESA is a short-acting or long-acting agent.

The ACM advised that the increased risk of cardiovascular and thromboembolic events in patients receiving ESAs should be appropriately covered in all PIs. The prothrombogenic effects of ESAs increase with increasing haemoglobin levels. A boxed warning could address increased mortality in patients with chronic kidney disease and that haemoglobin levels should not exceed 120 g/L.

Further information

For further information on the Advisory Committee on Medicines, please visit: Advisory Committee on Medicines or contact the ACM Secretary by email: ACM@health.gov.au.