Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement 6 – Thursday 30 November – Friday, 1 December 2017

Section A: Submissions for registration

The committee's advice was sought on 11 new pre-market applications for prescription medicines. The applications (table below) included four associated with Type A – new Chemical/Biological entities or a Biosimilar, 1 Type A – New Fixed dose combination, 5 associated with Type C – extension and indications and 1 application relating to a new generic medicine application (Type D).

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 A - New fixed combination	For general consideration
5	Type C - Extension of indication	For consideration of broader indication with or without substantiating supportive evidence.
1	Type D – New generic medicine	For general consideration

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: Pharmacovigilance

One pharmacovigilance item was referred to the committee for its advice.

General anaesthetic agents and paediatric neurotoxicity

The ACM was asked to provide advice on the safety of general anaesthetic agents administered to children.

The anaesthetics of interest can be administered by inhalation (desflurane, isoflurane and sevoflurane) or by intravenous injection (thiopental, ketamine, midazolam, propofol and

phenobarbitone). These medicines will be referred to as GAAs (general anaesthetic agents). Each agent has specific indications for use, which may include sedation and/or induction and/or maintenance of general anaesthesia. GAAs are used in a range of procedures and situations such as surgery, in diagnostic procedures that require immobility (e.g. for a MRI scan), for distressing procedures (e.g. change of burns dressings), and in intensive care. Non-surgical uses may be brief but may need to be repeated on multiple occasions. About 5% of children require anaesthesia at some time.

Neurotoxicity is a general term that refers to problems during the development of the brain and nervous system. There are various tests and scales to assess childhood neurological development.

The ACM considered a review by the United States Food and Drug Administration (FDA) that examined studies that investigated the effects of GAA exposure in the young. The FDA concluded there was sufficient evidence to warrant changes to the product information of relevant sedative medicines and GAAs. In America the warnings and precautions for these agents now refer to possible effects on brain development from repeated or lengthy (over 3 hours) surgeries or procedures in children younger than 3 years of age. (Note: The FDA review also refers to pregnant women during their third trimester. However, regional anaesthesia used during labour and delivery was outside the scope of the ACM discussion and the committee noted that general anaesthesia is rarely used in late pregnancy.)

The committee noted that substantial developmental changes occur in the nervous system before three years of age, which is the period of concern to the FDA.

The ACM noted that interim results of one ongoing trial and results from another trial indicate that relatively brief exposure to GAAs in otherwise healthy children was unlikely to cause clinically detectable deficits in cognitive function or behaviour.

The ACM advised that to date there is plausible animal evidence that exposure to GAAs or sedatives during late pregnancy or in young animals may result in long-term neurocognitive deficit. However, the relevance to humans is unclear.

The ACM advised that the studies in humans provide weak evidence of a link between GAAs and neurotoxicity in children. Some studies found an association and some studies found no association. Analysis of studies of GAA in children is complex: the procedure itself may cause harm; the circumstance necessitating the procedure may be associated with poor neurobehavioural outcomes; there needs to be sufficient duration of follow-up observations; post-operative pain management may have an influence; and the role of inflammation needs to be considered. The effects of dose and duration of anaesthesia were not clear. The ACM could not provide definitive advice based on currently available evidence from human studies.

However, the ACM advised that there is probably sufficient evidence (of at least a small risk) to continue with a cautious approach and to use anaesthetics for children only when necessary and for the shortest duration. The committee was aware of changing clinical practises to delay procedures where appropriate.

The committee noted that the Product Information (PI) documents for GAAs often have insufficient information on paediatric use, including precautions. The ACM agreed that accurate and contemporary PI documents were a regulatory ideal. However, the ACM also noted that as GAAs were long established in use in Australia the PI may no longer be the primary source of information for medical practitioners. The committee highlighted that any changes to PIs should reflect the body of evidence available for GAAs as a class.

The ACM advised that consideration could be given to possible options for further risk reduction, including:

- a statement on the TGA website on GAAs as a class, responding to the FDA position and the mixed evidence currently available
- discussions with and risk communications directed to relevant clinician groups, including on clinical considerations in the use of GAAs for surgery and diagnostic procedures in children.

The ACM suggested more definitive studies to address the current gaps in knowledge would help to better characterise potential risks as theoretical or of practical clinical concern.

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.