Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement 3 - Friday 2 June 2017

Section A: Submissions for registration

The committee's advice was sought on seven new pre-market applications for prescription medicines. The applications (table below) included five for Type A – new Chemical/Biological entities and 2 associated with Type C – extension and indications.

Number of applications	Application Type	Main consideration by ACM (among other items)
5	Type A - New Chemical /Biological Entity	For general consideration
2	Type C - Extension of indication	For consideration of broader indication without substantiating supportive evidence.

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. Browse all AusPARs.

Section B: Pharmacovigilance

One pharmacovigilance item, on gadolinium-based contrast agents (GBCAs) and bioaccumulation in the brain, was referred to the committee for its advice.

GBCAs are diagnostic agents used to enhance Magnetic Resonance Imaging (MRI) examinations. There are eight GBCAs approved for supply in Australia. Depending on their chemical structure, GBCAs are classed as either linear, in ionic or non-ionic forms, or macrocyclic, in ionic or non-ionic forms.

The ACM noted an increasing body of scientific evidence that gadolinium may accumulate in certain areas of the brain in patients who have been administered GBCAs. There is also evidence to suggest that linear GBCAs have a greater propensity to accumulate in brain tissue compared to macrocyclic GBCAs. To date, no clinical adverse effects have been confirmed in the literature in association with bioaccumulation of gadolinium in the brain.

Internationally, regulators have adopted different regulatory stances to this issue.

Background

Gadolinium is used intravenously to increase the MRI signal from hypervascular (neoplastic or inflammatory) lesions and blood vessels. The GBCAs differ in indications and age group of patients, and pharmacokinetic properties.

Current evidence suggests that small amounts of both linear and macrocyclic agents may distribute into certain areas of the brain, and that linear agents are retained in the brain tissue for longer periods of time than macrocyclic agents.

It is estimated that GBCAs are used in 30-40% of clinical MRI examinations.

GBCAs are generally regarded as very safe. The agents may cause minor reactions (nausea, headache, taste disturbance); skin rashes; and anaphylactic reactions (anaphylaxis occurs at rates of 1/10,000; fatal events are less than 1 in a million).

Safety issue

The ACM advised that the theoretical consequences of gadolinium retention in the brain could include potential effects on movement, vision, speech, cognition and behaviour.

Patient groups where accumulation of gadolinium in the brain may be higher include:

- paediatric patients (immature and more permeable blood brain barrier, and increased vulnerability of immature/growing brain cells to toxic insults). Developmental immaturity could mean that potential clinical effects (e.g. on movement, vision, speech, cognition, behaviour etc) will not be apparent or manifest until much later after exposure, and the relationship to GBCA may not be recognised.
- elderly patients (moderate blood brain barrier breakdown occurs with normal ageing)
- patients undergoing repeat scans (e.g. breast cancer surveillance)
- patients with inflammatory or demyelinating CNS diseases
- patients with renal impairment
- pregnancy (gadolinium crosses the placenta).

Differing opinions were expressed with regards to whether linear agents should continue to be used in paediatric and other high risk groups. Some participants were reassured by the long history of use of linear agents in these higher risk populations without any evidence of adverse effects. However, it was also noted that avoiding linear agents in these higher risk groups may be prudent, given that macrocyclic agents can be used as an alternative, and subtle clinical adverse effects may be difficult to detect from observational data.

Overall, the committee advised that encouraging more judicious use of these agents (linear and macrocyclic) is appropriate, given the current state of evidence.

The ACM noted that linear GBCAs have been used widely for over 30 years. During this extended time, there is no evidence of a clear clinical signal that correlates with gadolinium retention in the brain for any of the GBCAs, and there is no clear evidence as to whether deposition at the levels observed has any biological effect.

However, the committee noted that spontaneous adverse event reports for delayed and subtle effects would not be a sensitive way of detecting possible cases and so should be considered an incomplete source of information on this issue.

The ACM considered whether macrocyclic GBCAs are associated with a higher rate of hypersensitivity reactions than linear agents. The committee noted that interpretation of adverse event data is hindered by varying definitions of 'hypersensitivity' and the rarity of serious events. Theoretically, non-ionic agents could be claimed to be less likely to trigger mast cell degranulation (by analogy with iodinated contrast agents for CT). However, data for gadoteridol (non-ionic macrocyclic) do not fit well with this hypothesis. The committee advised that overall there was no convincing evidence to support the use of linear agents rather than macrocyclic agents to reduce the rate of hypersensitivity reactions.

The committee advised that, on balance and at this time, it supported risk mitigation including:

- update Australian Product Information document, to remove statements that GBCAs do not cross the blood brain barrier
- promote more judicious use of GBCAs
- targeted communication with professional bodies on the current status of evidence, that while there is evidence of accumulation in the brain, there is no evidence of clinical harms documented to date (noting the limitations of spontaneous reports as an incomplete source of definitive information on this issue)
- encourage dissemination of information to neurologists, general practitioners, paediatricians, oncologists and radiologists
- all clinical sites should be prepared to manage anaphylactic reactions, irrespective of what GBCA is used.

Further studies are needed to evaluate the potential clinical outcomes of accumulation of gadolinium in the brain.

Other items

In addition to pre-market items and pharmacovigilance item, ACM also considered the draft Therapeutic Goods Order (TGO) 80 – Child Resistant Packaging Requirements for Medicines 2017.

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.