Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement – Meeting 13, Friday 1 February 2019

Section A: Submissions for registration

The advice of the Advisory Committee on Medicines (ACM) was sought on six pre-market applications for prescription medicines, as tabulated below.

Number of applications considered	Application Type	Main consideration by ACM
1	Type B – New fixed dose combination containing one new chemical entity	For general consideration
3	Type C - Extension of indications	For general consideration
2	Type D – New generic medicine	For advice relating to the formulation

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: Post-Market items referred for advice

Two post-market items were referred for advice.

Thiopurines and TPMT testing

The ACM was asked to provide advice on the screening of patients prior to the administration of thiopurines.

Thiopurines are a class of medicines; the medicines discussed were azathioprine, mercaptopurine and tioguanine. These medicines are available under multiple brand names. Thiopurines are used for immunosuppression and are used in patients with organ transplants, acute leukaemia, severe rheumatoid arthritis, severe dermatological conditions and a range of other conditions.

Part of the known toxicity profile of thiopurines is a decrease in the number of white blood cells (leukopenia) and bone marrow suppression (myelosuppression), which can lead to severe and fatal infections.

Persons who have a deficiency in the thiopurine methyltransferase (TPMT) gene are particularly susceptible to thiopurine toxicity. Persons with the gene deficiency do not make enough, or any, of the enzyme needed to metabolise the thiopurine medicine.

Testing for deficiency of the TPMT gene requires a blood test; this testing is available in Australia. There are various degrees of deficiency of the TPMT gene; a major deficiency occurs in about 1 in 300 people.

Regardless of the result of TPMT testing, regular monitoring of white blood cell counts is required in all patients commenced on a thiopurine in order to monitor for drug toxicity.

The ACM discussed a number of studies, including a study by Coenen et al[1] in patients with inflammatory bowel disease. This study found no difference in the incidence of blood (haematologic) adverse events between the patient groups who were screened or not screened for TPMT genotype. For patients with deficient TPMT, standard thiopurine doses were associated with more frequent hematologic adverse events than when the dose was adjusted based on TPMT testing.

The ACM also discussed unpublished work by the TGA, a data linkage study on the relationship between Pharmaceutical Benefits Scheme-subsidised dispensing of a thiopurine medicine and Medicare Benefits Schedule (MBS)-subsidised testing for the TPMT gene.

Members advised that within Australia and internationally there are different clinical practices as to whether TPMT testing is undertaken prior to prescribing thiopurines. For example, guidance documents of different clinical specialties, clinical trial protocols and standard textbooks can take the approach that TPMT testing should be 'mandatory', 'recommended', 'optional' or 'where possible'. The diversity of approaches in Australia is also seen internationally, with Fargher et al reporting dermatologists undertaking significantly more enzyme testing than gastroenterologists or rheumatologists.[2]

The committee advised that mandatory TPMT genotyping prior to thiopurine treatment was not supported for the following reasons:

- The majority of episodes of myelotoxicity occur in patients with the wild type (normal) TPMT gene. That is, TPMT testing only identifies a small proportion of individuals at increased risk of haematological toxicity.
- There is little evidence to suggest that TPMT genetic testing reduces toxicity in practice at the population level.
- Testing for TPMT genotype does not necessarily predict TPMT enzyme activity.
- Myelotoxicity increases with increasing patient age.

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[1] Coenen MJH, de Jong DJ, van Marrewijk CJ, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. Gastroenterology, 2015. 149:907-917. doi: 10.1053/j.gastro.2015.06.002

[2] Fargher EA, Tricker K, Newman W, et al. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. Journal of Clinical Pharmacy and Therapeutics 2007. 32, 187–195. doi: 10.1111/j.1365-2710.2007.00805.x

The committee advised that changes to the Product Information (PI) for thiopurine medicines could contribute to improved patient management. Changes to the PIs should include:

- TPMT testing is strongly recommended (but not mandatory)
- haematological monitoring of patients on thiopurines is critical, particularly early in the treatment period and in elderly patients
- recognition that TPMT testing is now available via pathology laboratories and genetic testing services as an MBS-subsidised service.

The committee advised that targeted communications with specialty groups should be undertaken, to highlight the following educational messages:

- the importance of education for patients on immunosuppressants
- the importance of regular monitoring of the patient's wellness as well as blood counts
- the importance of education for patients on the symptoms of a medical emergency and the actions to take, including out-of-hours and away from urban centres and when to attend a hospital emergency department
- patient age as a risk factor for leukopenia, and that patient age should be taken into consideration in any clinical guidelines on TPMT testing
- diagnosis of sepsis and its management.

Gabapentinoids and risk of harmful and hazardous use

The ACM was asked to provide advice on the safety of pregabalin and gabapentin ('gabapentinoids').

These medicines are available under multiple brand names.

Gabapentin and pregabalin have TGA-approved indications for epilepsy, mainly as add-on therapy for partial seizures in adults and, for gabapentin, also in children. However, the committee noted that there are alternative medicines available that may be preferred for efficacy and tolerance.

The gabapentinoids also have TGA-approved indications for neuropathic pain.

The committee noted that off-label use is occurring in Australia for non-neuropathic pain and generalised anxiety disorder.

From analysis of the database of adverse events reported to the TGA, a safety signal for the harmful and hazardous use (also known as misuse or abuse) of gabapentinoids, in particular pregabalin, has been detected. The adverse events reported to the TGA include deaths.

Harmful and hazardous use can include the development of tolerance, taking higher doses than prescribed, drug-seeking behaviour and intentional and accidental poisonings. An analysis of pregabalin adverse events based on 38 clinical trials found that euphoria was experienced by 5% of all patients taking the medicine.[3]

[3] Zaccara G, Gangemi P, Perucca P, et al. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011; 52:826-36. doi: 10.1111/j.1528-1167.2010.02966.x

The TGA has corroborated the safety signal with data from the NSW Poisons Information Centre (NSW PIC), the National Coronial Information System (NCIS) and NPS MedicineWise. There is now also high quality international evidence on harmful and hazardous use.

The committee noted the following points.

- Premarket studies for pregabalin suggested a low potential for abuse; such studies commonly exclude people with a history of substance abuse.
- Some people are at higher risk of harmful and hazardous use of pregabalin: people with depression, people who concomitantly use opioids and/or benzodiazepines, and young men.
- Pregabalin appeared to have a higher addictive potential than gabapentin.

The committee considered there to be sufficient and compelling evidence of a strong signal for the harmful and hazardous use of pregabalin.

The committee noted that the evidence included multiple sources from Australia and internationally, including data regarding fatalities, drug utilisation, prescribing patterns, adverse event reporting, and trends in intentional poisonings.

The committee accepted the conclusion of Cairns et al[4]: 'One in seven Australians dispensed pregabalin appears to be at high risk of misuse'.

The committee noted that pregabalin may have a higher potential for dependence and abuse than gabapentin because it is more rapidly absorbed, has a higher affinity for the α2-δ subunit of presynaptic voltage-gated calcium channels, and has a longer half-life. Notwithstanding differences in patterns of abuse of gabapentin to date, the committee advised that if strengthened risk minimisation strategies were to be put in place only for pregabalin then there could be a shift to the use of gabapentin. Overall, the committee advised that pregabalin and gabapentin should be treated as a class for the purposes of risk minimisation activities.

The ACM discussed regulatory mechanisms for minimising the risk of hazardous and harmful use associated with gabapentinoids. The ACM advised that a multifaceted approach to harm reduction could include the following options:

- changes to the Product Information (PI) for pregabalin and gabapentin to prominently address the risk of hazardous and harmful use including risk factors and discontinuation advice
- a targeted and coordinated professional education strategy, to ensure prescribers are aware of the current concerns around harmful and hazardous use and understand the full extent of this problem. This could include a TGA web statement, liaison with NPS MedicineWise, and/or collaboration with the relevant clinical colleges.

The committee also discussed other mechanisms for minimising the risk of hazardous and harmful use, including potential changes to the Poisons Standard and/or the Pharmaceutical Benefits Scheme entries for pregabalin and gabapentin.

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.

[4] Cairns R, Schaffer AL, Ryan N, et al. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. Addiction 2018. doi:10.1111/add.14412