Advisory Committee on the Safety of Medicines

Meeting statement

Meeting 32 – 10 March 2016

Role of the Advisory Committee on the Safety of Medicines (ACSOM) in the TGA’s regulatory decision making process

The ACSOM is a statutory advisory committee established by the Therapeutic Goods Regulations 1990.

The TGA currently has eleven statutory advisory committees from which it can obtain independent expert advice on specific scientific and technical matters to aid the TGA’s regulatory decision making and other regulatory processes. The ACSOM provides advice to the TGA on, amongst other things, matters relating to the safety, risk assessment, risk management and other matters related to pharmacovigilance of medicines.

How this statement should be read

The advice provided by the ACSOM is an important element in the undertaking of the regulatory functions of the TGA. However, it forms only one part of the total body of information that is available to, for instance, a TGA delegate making a regulatory decision under the Therapeutic Goods Act 1989 (‘the Act’). Therefore, while appropriate consideration will be given to such advice, it is important to note that neither the TGA nor a TGA delegate is obliged to follow it.

It should also be noted that details of the committee’s advice may not become publicly available for some time after the committee has provided that advice. The purpose of this Meeting Statement is to describe in general terms the matters considered by the committee at each meeting and for it to be available as soon as reasonably practical after the relevant meeting.

Additionally, following publication of this statement, it is most likely that further work will be undertaken by the TGA to investigate, monitor and/or evaluate the medicines considered by the ACSOM; and this will continue for some time into the future. It is therefore possible that further information about the medicines will become publicly available at a later time and this will be pursuant to a regulatory decision under the Act being made and following further consultation with the medicine’s sponsor and/or manufacturer.
Overview of the safety reviews and therapeutic goods referred for advice

The TGA continually monitors therapeutic goods supplied in Australia to ensure their ongoing safety, efficacy and quality. As part of this process, the TGA routinely undertakes safety reviews of therapeutic goods.

At this meeting, the committee’s advice was sought on the following safety review.

Codeine – safety and efficacy review

Background

This safety review related to those medicines that contain codeine and which can be supplied over-the-counter (OTC). The medicines vary in strengths, dosage form, combinations with other active ingredients, and indications for use. Codeine or its salts, especially the phosphate, can be used for the treatment of coughs and colds, non-productive cough, mild to moderate pain and the symptomatic relief of acute diarrhoea.

Codeine is metabolised to morphine. Codeine demonstrates marked variability in its rate of transformation to morphine in different individuals, with the potential for severe toxicity in ultra-rapid metabolisers and a lack of efficacy in slow metabolisers. The safety of codeine was reviewed at the ACSOM 28 meeting, held July 2015, to address concerns on its use in children and use by people who are ultra-rapid metabolisers.

Scheduling status

Codeine is available in Australia under the arrangements stated in the \textit{Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)}.

As at February 2016, there were 216 medicines registered in the Australian Register of Therapeutic Goods (ARTG) that were scheduled Schedule 2 (S2) or Schedule 3 (S3).

Codeine is only available OTC when formulated in combination with other active ingredients.

The ACSOM noted that consideration is currently being given to a \textit{proposal to up-schedule low dose codeine containing products currently available as S2 and S3 medicines to Schedule 4 (Prescription Only) medicines}. The ACSOM was not asked to provide advice on the scheduling of codeine, which is the role of the \textit{Advisory Committee on Medicines Scheduling (ACMS)}.

Review of the efficacy and safety of codeine ('the review')

In early 2016 the TGA commissioned The George Institute for Global Health to undertake a review of the safety and efficacy of low dose codeine containing products. The review, entitled \textit{’Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine based antitussives’}, was a systematic review which aimed to determine the efficacy and safety of OTC codeine combination analgesics (CCA) for the treatment of any pain condition or as an antitussive (suppresses coughing).

The committee was asked to comment on whether the review provided evidence for the benefit-risk balance for low-dose codeine as an analgesic and as an antitussive.

The ACSOM advised that the studies covered in the review were limited, including that:
• the specific incremental effect of the codeine, above and beyond that of the paracetamol or other non-steroidal anti-inflammatory drug (NSAID) present in the CCA, was not able to be quantified from the evidence given in the review

• there were inadequate data on the frequency of adverse events, and it was unstated as to whether the adverse events were specific to the codeine or NSAID components of the medicines

• patients in the reviewed studies were mostly under the care of a healthcare professional e.g. post-surgery, and were therefore unlike consumers self-selecting S2 analgesia for conditions such as tension headache or musculoskeletal pain

• patients in the reviewed studies were mostly young and the studies were of limited duration.

Overall, the ACSOM agreed that there was limited evidence of additional incremental efficacy of codeine in the review and this made it difficult to assess the overall benefit-risk balance of codeine.

Robust quantitative data were lacking on: the proportion of CCA users who were likely to be experiencing problems with opiate dependence or abuse; the likely incidence of CCA-related and codeine-related harms; and the level of need which is met by CCAs that are available OTC. Data were also limited on the efficacy of CCAs versus potential replacement products in the community setting.

The committee was also asked to provide advice on any alternative or additional risk mitigation activities for CCA.

The committee noted that current controls on the availability of codeine reflect its long history of use in particular medical and cultural environments, and also reflect a balance between the provision of pain relief for the individual and public health concerns on the misuse and harms of opiates in the population. The committee also noted that, to date, risk mitigation activities to limit abuse while allowing continuation of OTC availability of CCA have included limiting the maximum daily dose, limiting the maximum pack size, limiting the quantity of codeine per dosage unit or the concentration in an undivided preparation, and the prohibition on the advertising of codeine-containing S3 medicines to consumers.

The committee identified the following risk mitigation activities for further consideration by the TGA:

• imposing further limitations upon the pack size, including only permitting supply for a single day

• real-time monitoring of the supply of CCA, similar to existing arrangements which have been implemented under Project Stop to prevent the unlawful diversion of pseudoephedrine.

The committee advised that the effect of these steps would be to increase the number of opportunities for a healthcare professional to engage the consumer in conversation on pain management therapies. This could be via conversations with a pharmacist in relation to OTC supply, or with a medical practitioner when obtaining a larger (S4) supply.

The committee’s advice has been provided to the TGA for consideration as part of the TGA’s regulatory decision making processes.
Risk management plans

A Risk Management Plan (RMP) is a set of pharmacovigilance activities and interventions designed to identify, characterise and manage risks relating to a medicine.

At this meeting, there were no RMPs referred to the committee for its advice.

Further information

Meeting statements are made publicly available after each meeting.

For further information on the ACSOM, please visit the ACSOM webpage or email acsom@tga.gov.au