Australian Government

Department of Health

Therapeutic Goods Administration

Advisory Committee on the Safety of Medicines

Meeting statement

Meeting 28 – 10 July 2015

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 ten 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 use in children and ultra-rapid metabolisers

The committee noted that currently there are over 300 codeine-containing medicines which are approved for supply in Australia. They cover various dosage forms, strengths, combinations with other active ingredients, and indications for use, and include prescription and over-the-counter (OTC) preparations. The safety review considered by the committee addressed two risks: use in children, and use in persons who are ultra-rapid metabolisers of codeine.

Codeine use in children

Currently, some OTC products that contain codeine are indicated for use in children as young as one year of age. Children are more susceptible to respiratory problems than adults due to their immature airway anatomy. Children who have undergone tonsillectomy/ adenoidectomy ('adenotonsillectomy') for obstructive sleep apnoea may be additionally susceptible to opioid-induced respiratory depression in the post-operative period.

Morphine (the active metabolite of codeine) can also be ingested by infants through breast milk, leading to a risk of respiratory depression in infants of ultra-rapid metaboliser mothers who take codeine whilst breastfeeding. Deaths have been reported internationally in such infants, and warnings regarding this risk have been issued by overseas regulators[1,2]. Administration of codeine to children of any age for analgesia is not in keeping with current World Health Organization (WHO) guidelines for paediatric analgesia.[3]

Codeine use in ultra-rapid metabolisers

Codeine's analgesic effect is dependent on its conversion to morphine. However, there is a wide variability in response to codeine and these can be categorised into four broad groups - 'ultra-rapid metabolisers' (who form morphine rapidly, leading to a higher risk of toxicity), 'extensive metabolisers' (the majority of the population who are suited to the recommended doses), 'intermediate metabolisers' (who have reduced morphine formation and therefore recommended doses may or may not provide analgesia) and 'poor metabolisers' (who account for up to 10% of patients and for whom codeine is ineffective).

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[1] FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. <http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm>

[2] EMA/441891/2013 Assessment report for codeine-containing medicinal products indicated in the management of pain in children <http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Codeine_containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500147065.pdf>

[3] World Health Organization. Persisting pain in children package: WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. 2012

The prevalence of codeine ultra-rapid metabolism in children is not known, but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolism is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%–10% in Caucasians. The highest prevalence (16%–28%) occurs in North African, Ethiopian and Arab populations.[4]

The TGA completed a review of codeine safety in the context of ultra-rapid metabolism of codeine to morphine by children and breastfeeding mothers. The main conclusions of the review were that the risks associated with ultra-rapid metabolism of codeine are not consistently and adequately addressed across all codeine-containing products.

ACSOM agreed that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years. There is no practical method for testing for metaboliser status, including it not being possible to predict a child's metaboliser status based on parental experience or ethnicity. Prior exposure to codeine without reported adverse events was not definitive of metaboliser status, as the parent/carer may not have distinguished between a settled child with adequate analgesia (who may be an extensive or intermediate metaboliser) and a chemically sedated child with high levels of morphine (who may be an ultra-rapid metaboliser).

As it is not possible to identify in advance the subgroup of children who are at increased risk of toxicity (e.g. through being an ultra- rapid metaboliser), the committee's advice relates to the risks for all children under the age of 12.

ACSOM also agreed that the risks associated with codeine outweigh the benefits of codeine for analgesia in children under the age of 18 years who have undergone tonsillectomy or adenoidectomy for sleep apnoea, for the same reasons as for children under the age of 12 years, as above. This is consistent with the United States Food and Drug Administration (US FDA) position that codeine use after adenotonsillectomy is contraindicated[5]. The committee also noted that there have been a number of adverse event cases observed that are not clearly explained but may relate to sleep apnoea.[6]

ACSOM also agreed that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers.

As a mother's knowledge of her own experience with codeine (and indirectly, metaboliser status) does not predict the infant's response, breastfeeding should be a contraindication for codeine.

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[4] Sistonen J, Sajantila A, Lao O et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenetics and Genomics 2007; 17:93-101. doi: 10.1097/01.fpc.0000239974.69464.f2

[5] FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy <http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm>

[6] FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy <http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm>
See also Kelly LE, Sommer DD, Ramakrishna J et al. Morphine or Ibuprofen for Post-Tonsillectomy Analgesia: A Randomized Trial. Pediatrics 2015; 135:307-313. doi: 10.1542/peds.2014-1906. This study demonstrated a dramatic difference between oxygen desaturation on the first postoperative night in children assigned to morphine analgesia compared to ibuprofen.

The committee was undecided whether the risks associated with ultra-rapid metabolism of codeine outweigh the benefits of codeine for any indication in ultra-rapid metabolisers of any age. There are some indications for codeine (e.g. cancer pain, diarrhoea and cough) where codeine may be useful in ultra-rapid metabolisers. Additionally, adults will generally know how well codeine works for them and have the capacity to self-regulate by adjustments to the dosage regimen. Nonetheless, the committee agreed with published position statements that a reduction of codeine use in the community would be beneficial.[7]

ACSOM noted the following contraindications which were recommended in the TGA's safety review to be included in the codeine Product Information - use in children under the age of 12 for any reason; use in people of any age known to be ultra-rapid metabolisers; use in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea; and use by breastfeeding mothers. The Committee also advised the TGA to consider the additional risk minimisation actions described below.

The committee noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe. Therefore, communication of the contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction. Additional measures including education and the possible rescheduling of codeine-containing medicines also needed to be considered. The committee supported consistency and harmonisation in labelling across all codeine-containing medicines, especially regarding advice to breastfeeding mothers.

ACSOM also advised that education messages on the risks to infants of breastfeeding mothers needed to be targeted to the relevant professional colleges (e.g. via reference to the index case[8]), as well as to consumers. Such messages should emphasise that codeine is a 'prodrug', it is metabolised to morphine, and should therefore be treated with the same care as morphine.

Education messages need to be strong and balanced, and focus on information about patients in whom codeine is unsafe (e.g. ultra-rapid metabolisers) as well as patients in whom codeine is ineffective (e.g. poor metabolisers). Renal function and drug interactions also needed to be considered prior to any administration of codeine.

The committee also advised that consideration be given to whether the continued supply of paediatric formulations containing codeine was appropriate and safe for the community. Liquid formulations containing codeine, other than paediatric formulations, would need to remain available for adults with difficulties in swallowing and for easy dose titration, and labelling would need to be clear that the liquid formulation was not to be used for children.

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[7] For example, the National Pharmaceutical Drug Misuse Framework for Action states:
… the misuse/poor quality use of medicines occurs on a spectrum ranging from those who unintentionally misuse these medications in response to inappropriate prescribing practices, through to those who intentionally obtain and misuse medications for their non-therapeutic effects and/or for financial gain. Problems may also emerge with over the counter codeine-containing medications, if they are taken in quantities that lead to codeine dependence or health problems associated with consuming large doses of ibuprofen or paracetamol which can also be found in analgesics containing codeine.
<http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/9C52D7D6E2C14A72CA257C3F001F009D/$File/National%20PDM%20Framework.pdf>

[8] Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006: 368:704. doi:10.1016/S0140-6736(06)69255-6

Activities to reduce the use of codeine cannot occur in isolation from consideration of alternative pain management strategies. Pain management strategies that do not include codeine needed to be carefully defined and their implementation carefully considered. For example, direct administration of morphine could be considered as an alternative and the issues of analgesic polypharmacy and escalation up the 'pain ladder' also require consideration in the development of any pain management strategies that omit codeine.

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, the committee's advice was sought on seven RMPs for medicines with proposed indications relating to:

- neoplastic disorders
- infectious diseases
- vascular disorders.

For these medicines, which included one generic medicine, the committee was asked to provide advice on matters including:

- the adequacy of safety concern lists provided by the sponsors, where omitted safety concerns may be considered to be class effects
- the completeness of the adverse events listed in a table of ongoing safety concerns
- the adequacy of pharmacovigilance plans / activities intended to mitigate all safety concerns or monitor the risks associated with the medicine(s) and what, if any, additional pharmacovigilance activities would be appropriate to monitor those risks (e.g. surveillance of clinical isolates to determine local epidemiological data)
- the adequacy of the proposed design and conduct of a planned post-marketing pharmacoepidemiology study and if possible, how it could be improved
- the adequacy of risk minimisation plans / activities intended to mitigate all the safety concerns / risks of the medicine(s) and in particular, their adequacy to manage specified identified risks
- if those risk minimisation plans were not considered to be adequate, what other additional risk minimisation activities might be required (e.g. managed distribution program; relevance of United States Food and Drug Administration's Risk Evaluation and Mitigation Strategies).

The committee's advice will shortly be provided to the TGA for consideration as part of the TGA's regulatory decision making processes.

Following complete assessment of the application, information on the RMP evaluation will be included in the Australian Public Assessment Reports (AusPAR), which is published on the TGA website once it is finalised.

Further information

Meeting statements are made publicly available after each meeting.

For further information on the ACSOM, please visit: the ACSOM webpage or contact the ACSOM Secretary: Mr Craig Davies by phone on 02 6232 8641 or email: acsom@tga.gov.au