



Advisory Committee on Medicines

Meeting Statement 7 – Thursday 1 February – Friday, 2 February 2018

Section A: Submissions for registration

The committee's advice was sought on nine new pre-market applications for prescription medicines. The applications (table below) included five associated with Type A – new Chemical/Biological entities or a Biosimilar and 4 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/Biosimilar	For general consideration
4	Type C - Extension of indication	For consideration of broader indication with or 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. To browse all AusPARs see: <<https://www.tga.gov.au/browse-auspars-active-ingredient>>

Section B: Pharmacovigilance – Section B: Pharmacovigilance

Two pharmacovigilance items were referred to the committee for its advice.

Modified release paracetamol and overdose

The ACM was asked to provide advice on the safety of modified release paracetamol products, following a recent reconsideration of the medicine in Europe.

Paracetamol 665 mg in modified release formulations is available under several brand names with approved indications including relief from persistent pain for up to 8 hours and relief of persistent pain associated with osteoarthritis and muscular aches and pains such as backache. The standard dose of modified release paracetamol is two tablets three

times daily. This dosing is more convenient than standard immediate-release paracetamol 500 mg products, which require four times daily dosing.¹

Paracetamol (including all strengths and formulations) is involved in

a large proportion of accidental paediatric exposures and deliberate self-poisoning cases and is the leading pharmaceutical agent responsible for calls to Poisons Information Centres in Australia and New Zealand. Paracetamol is also the single most commonly taken drug in overdoses that lead to hospital presentation and admission. Hepatic failure and death are uncommon outcomes, although paracetamol remains the most important single cause of acute fulminant hepatic failure in Western countries.²

The ACM considered a recent recommendation of the [European Medicines Agency \(EMA\) Pharmacovigilance Risk Assessment Committee \(PRAC\)](#)³ to suspend modified release paracetamol from marketing as the benefit-risk balance of modified release paracetamol is no longer favourable. The advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine. Treating physicians may not know whether an overdose of paracetamol involves immediate-release or modified release product, making it difficult to manage the overdose. The PRAC could not identify sufficient means to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across Europe to allow for treatment of cases that involve modified release paracetamol preparations.

The committee noted that the PRAC report had identified 319 spontaneous adverse event reports of overdose. Of these 319 cases, almost all were from Sweden (67%) and Australia (31%). The majority of patients recovered or improved while 2 patients needed liver transplants. There were 5 fatal cases reported out of the 319 cases.

The committee noted [an Australian study](#)⁴ that has confirmed several features of modified release paracetamol overdose that make patient management difficult: toxic levels requiring administration of acetylcysteine (the antidote) subsequent to two non-toxic levels of paracetamol (which would usually permit discontinuation of the antidote); double paracetamol peaks; and the need to extend use of the antidote beyond the standard 21 hours.

Based on the information available to the committee on efficacy and also on safety in overdose, the benefit to risk ratio of modified release paracetamol may be marginal.

¹ The committee did not discuss the safety of immediate-release paracetamol in overdose. The advice provided by the committee was not in relation to immediate-release paracetamol.

² Guidelines for the management of paracetamol poisoning in Australia and New Zealand (web)

https://www.mja.com.au/sites/default/files/issues/203_05/Guidelines_paracetamol_Aus_NZ_2015.pdf

³http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/12/news_detail_002876.jsp&mid=WC0b01ac058004d5c1

⁴ [The study](#) was published subsequent to the ACM meeting. The committee discussed the related abstract:

Chiew A, Isbister G, Page, C et al. Modified release paracetamol overdose: a prospective observational study. (2018): 16th Annual Scientific Congress of Asia Pacific Association of Medical Toxicology (APAMT) 8–10 November 2017, Kandy, Sri Lanka, Clinical Toxicology, DOI: 10.1080/15563650.2017.1399703

The ACM discussed regulatory mechanisms for minimising the risks associated with overdose. Possible options include:

- possible up-scheduling in the Poisons Standard
- reduction in non-prescription pack size as [evidence from the United Kingdom⁵](#) suggests that reduction in paracetamol pack size is associated with a fall in the incidence of overdose
- changes to product information to align with current guidelines on overdose management, noting that revised guidelines on the treatment of overdose are anticipated
- education and communication on pain management generally, including appropriate use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).

A potential benefit expected from the availability of modified release paracetamol was to reduce the use of NSAIDs and opiate analgesics. The committee was not aware of evidence that demonstrated a reduction in NSAID and opiate use since the introduction of modified release paracetamol in Australia or internationally.

Medicines containing ethinylestradiol 35 microgram and cyproterone acetate 2 mg, and off-label prescribing and risk of venous thromboembolism

The ACM was asked to provide advice on the safe prescribing of ethinylestradiol/cyproterone tablets, particularly when prescribed off-label, following recent media interest in this issue.

Tablets containing the fixed combination of ethinylestradiol 35 microgram and cyproterone acetate 2 mg have been available in Australia since 1992. There are several brand names for the medicine. This prescription-only medicine is approved to treat the signs of androgenisation in women, such as severe acne or hirsutism (excessive body hair). The ingredients also provide effective oral contraception; however, the medicine is not approved as an oral contraceptive in the absence of the need to treat signs of androgenisation.

The ACM considered that, when prescribed for the approved indication, the benefits of the medicine outweigh the risks, and the medicine has a useful place in clinical practice in Australia. The committee noted that data on why the medicine had been prescribed – either for symptoms or androgenisation or for contraception alone was limited in the recent media reports.

The ACM confirmed that it is not appropriate for ethinylestradiol 35 microgram and cyproterone acetate 2 mg to be prescribed off-label as an oral contraceptive for women who do not have signs of androgenisation as there are other effective hormonal contraceptives available that are indicated for this purpose.

The ACM advised that additional controls on prescribing ethinylestradiol/cyproterone tablets would not improve the safe and effective use of this medicine, when used for the intended indication and limiting prescribing to specialist endocrinologists, dermatologists and gynaecologists would disadvantage women with less easy access to specialists especially in rural and remote areas.

⁵ <http://www.bmj.com/content/346/bmj.f403>

Risk communication activities undertaken to date by the Therapeutic Goods Administration and [NPS MedicineWise](#)⁶ were appropriate.

The particular area of concern raised in the media was the occurrence of venous thromboembolism (blood clots) in young women.

The ACM noted that the background risk for thromboembolism in women of childbearing age is estimated as [1.9-3.7 per 10 000 woman-years](#)⁷. That there is an increased risk of thromboembolism with combined hormonal contraceptives has been known for some time, and the ACM noted the recent TGA [safety advisory on combined hormonal contraceptives](#)⁸ and the risk of blood clots. Women taking a combined hormonal contraceptive containing ethinylestradiol and cyproterone are at an increased relative risk of blood clot; however, the absolute excess risk is still small and is low compared to the risk of VTE during pregnancy.

The ACM noted contraindications and precautions in the use of combined hormonal contraceptives already include factors that are accepted to increase the risk of thrombosis. Some risk factors are modifiable (e.g. smoking). Non-modifiable risk factors include genetic mutations that are thrombogenic; that is, there are several genetic mutations, of difference prevalence rates in different populations, that are associated with increases in the rates of VTE. The ACM noted that the presence of a thrombotic mutation does not make a VTE inevitable, and that the presence of a marker of thrombophilia cannot be used in isolation to predict thrombotic risk. Factor V Leiden, which is usually tested together with activated protein C-resistance, is a weak marker of thrombophilia. Even a 30-fold increase on the baseline risk of VTE, as found by [Vandenbroucke et al](#)⁹, is an absolute risk of less than 1%.

Where a woman is known to have a thrombogenic mutation, or has a personal medical history that includes a VTE, use of a combined hormonal contraceptive is contraindicated. However, there is no current evidence that screening for thrombogenic mutations in women who have not had a VTE would be effective as risk minimisation, as screening defines a risk not a certainty. The risk of VTE for women on ethinylestradiol 35 microgram and cyproterone acetate 2 mg is low compared to the risk of VTE during pregnancy. The ACM noted that this is consistent with the guidelines of [The Royal Australian and New Zealand College of Obstetricians and Gynaecologists](#)¹⁰ (RANZCOG) on combined hormonal contraceptives.

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

- discussion with RANZCOG regarding continued development of its statement on combined hormonal contraceptives
- a stand-alone guidance on 'oral contraceptives and air travel'

⁶ <https://www.nps.org.au/medical-info/clinical-topics/news/combined-oral-contraceptive-pills-supporting-an-informed-choice>

⁷ http://www.cochrane.org/CD010813/FERTILREG_contraceptive-pills-and-venous-thrombosis

⁸ <https://www.tga.gov.au/alert/combined-hormonal-contraceptives>

⁹ <https://www.ncbi.nlm.nih.gov/pubmed/7968118>

¹⁰ <https://www.ranzcog.edu.au/>

- ethinylestradiol 35 microgram and cyproterone acetate 2 mg as a relevant case study in prescriber education on off-label prescribing.
- ongoing and wider education on off-label prescribing, noting the recent article published by the TGA on [off-label prescribing](#)¹¹.

Risk assessment (especially the distinction between absolute risk and relative risk), informed consent and agreed decision-making are critical in all prescribing decisions. For ethinylestradiol 35 microgram and cyproterone acetate 2 mg, appropriate prescribing for the registered indication followed by assessment of thrombotic risk, education on symptoms of thrombosis and enhanced follow up in the first year of use should be agreed by the prescribing practitioner and patient at the time of initial consultation. The ACM noted that it should be routine clinical practice that a decision to prescribe any oral contraceptive should also address modifiable risk factors for VTE (e.g. smoking).

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.

¹¹ <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-8-number-4-august-september-2017>