



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Advisory Committee on the Safety of Medicines

Meeting statement

Meeting 35 – 2 September 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 reviews.

### **Adverse safety signal**

The committee's advice was sought on a safety signal for a registered medicine, in the context of active submissions under evaluation by the TGA.

The committee was asked to provide advice on matters including:

- the appropriateness of proposed changes to the indications
- whether a patient registry would be beneficial
- possible inclusions in the Product Information such as a black box warning, patient monitoring and discontinuation rules
- whether access to the medicine should be restricted to patients with evidence of appropriate risk mitigation activities.

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

### **Testosterone and the risk of arterial and venous thromboembolism**

This safety review related to all testosterone-containing medicines registered in the Australian Register of Therapeutic Goods (ARTG) for use in Australia. As at August 2016, there were 23 testosterone-containing medicines registered in the ARTG.

Testosterone, the primary androgenic hormone, is responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics including muscle mass, bone mass and body hair. Testosterone is available in a range of esters, dosage forms and routes of administration (oral capsules, topical cream and gel and solution, transdermal patches, subcutaneous implant, intramuscular injection).

Other regulators have published information regarding testosterone products and the risk of arterial thromboembolism (ATE) (e.g. heart attack, stroke) and venous thromboembolism (VTE) (e.g. pulmonary embolism, deep vein thrombosis). The United States Food & Drug Administration has required precautionary statements to warn of the potential risk of ATE and VTE in information documents for testosterone-containing medicines. The European Medicines Agency did not recommend similar changes to the European Summary of Product Characteristics.

In view of these different approaches, the committee was asked to provide advice on specific questions asked by the TGA as to whether updates to the Product Information (PI) documents for testosterone-containing medicines are warranted.

The ACSOM was asked to advise whether there is sufficient evidence to warrant warning prescribers of the possible risk of ATE and VTE in the Australian PI for testosterone-containing medicines.

The committee noted that the evidence for an increased risk of ATE/VTE in men prescribed testosterone that has led other regulators to strengthen warnings has been

based on observational studies. The committee commented that it is not possible to reliably quantify the intended effect of treatment on outcomes using observational studies. Potential confounding (or reverse causality) resulting from variation in use of testosterone according to risk of cardiovascular disease (including that related to undiagnosed / preclinical disease) can only be addressed reliably in a randomised trial.

The committee noted that a systematic review and meta-analysis provided the best evidence, and referred to the study by Xu et al.<sup>1</sup> The committee advised that there was evidence of a weak signal of increased cardiovascular risks in general (but not for specific events) with use of testosterone-containing medications, sufficient to warrant a warning in the PIs for testosterone-containing medicines.

The committee advised that it was not appropriate to replicate the precautions required in America in full in Australian PIs at this time. The committee advised that adverse event information in the PIs should be updated.

Regarding whether any additional statements should be included in the PIs to address the potential for off-label use, the committee noted that international experience suggests that off-label use of testosterone is growing and will continue to grow, particularly by older age men to address ageing concerns and by younger age men for body-building. By definition, there is limited quality clinical evidence on uses that can be described as 'misuse' or 'abuse'. The committee advised that on balance the risk-benefit balance for off-label use was not known.

The committee advised that risks in the Australian context could be quantified via randomised clinical trials. The committee supported the undertaking of a range of risk minimisation activities to educate prescribers and the public.

## **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 four RMPs for medicines with proposed indications relating to:

- a haematological disorder
- a musculoskeletal disorder
- a renal disorder
- an infectious disease.

For these medicines, the committee was asked to provide advice on matters including:

- the adequacy of the proposed summary of safety concerns and whether there are any additional identified risks, potential risks or missing information that should be captured in the RMP
- the adequacy of the proposed pharmacovigilance plan (including monitoring of particular outcomes) and if not considered adequate, which additional activities might be required

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<sup>1</sup> Xu L, Freeman G, Cowling BJ, et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Medicine 2013; 11:108. doi: 10.1186/1741-7015-11-108

- the adequacy of the proposed risk minimisation activities (including proposals regarding healthcare practitioner education; dose escalation; presentation of the medicine) and if not considered adequate, which additional activities might be required.

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 applications, 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.

## **Other**

At this meeting, the committee's advice was also sought regarding an application for the use of a restricted representation in the consumer advertising and on the label of a product that is a listed medicine in the ARTG.

## **Further information**

Meeting statements are made publicly available after each meeting.

For further information on the ACSOM, please visit the [ACSOM web page](#) or email [acsom@tga.gov.au](mailto:acsom@tga.gov.au).