



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

ACCM 5

Advisory Committee on Complementary Medicines

Extracted Ratified minutes
Fifth meeting

4th March 2011

TGA Health Safety
Regulation

A decorative graphic at the bottom of the page consisting of several overlapping, curved bands in shades of blue and green, creating a wave-like effect.

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ACNM	Advisory Committee on Non-prescription medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADRs	Adverse Drug Reactions
ARTG	Australian Register of Therapeutic Goods
BP	<i>British Pharmacopoeia</i>
CMEC	Complementary Medicines Evaluation Committee
CG	Compositional Guideline
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
DoHA	Department of Health and Ageing
EU	European Union
MOU	Memoranda of Understanding
OCM	Office of Complementary Medicines
PI	Product Information
RASML	Required Advisory Statements for Medicine Labels
SATCM	State Administration of Traditional Chinese Medicine
SUSDP	<i>Standard for the Uniform Scheduling of Drugs and Poisons</i>
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
USP	<i>United States Pharmacopoeia</i>

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The Advisory Committee on Complementary Medicines (ACCM) held its fifth meeting at the TGA from 1:30 pm to 4:30 pm on 4th March 2011. This was a half day meeting following an induction program for new members of the Committee.

Members of ACCM present

Professor Alan Bensoussan (Chair)

Dr Lesley Braun

Ms Patricia Greenway

Ms Karen Martin

Professor Stephen Myers

Dr Richard Oppenheim

Dr Marie Pirotta

Dr Simon Spedding

Dr Xianqin Qu

Professor Bill Webster

Professor Peter Williams

Dr Hans Wohlmuth

Present from the Therapeutic Goods Administration (TGA)

Ms Jenny Burnett (Acting Secretary)

Dr Megan Keaney (Principal Medical Advisor)

Ms Diane Wilkinson

Present for part of the meeting:

Dr Linda Lenton

Ms Stephanie Williams

Dr David Tattersall

Ms Hongxia Jin

Dr Lay Khoon Choo

Mr Peter Holian

1. Procedural Matters

1.1 Opening of Meeting

The Chair opened the meeting at 1:30pm, welcoming ACCM Members and TGA staff.

1.2 Apologies

Mr Michael J Smith (Secretary).

1.3 Conflict of Interest

Members submitted conflict of interest declarations, specific to agenda items for this meeting, to the Chair.

2. Confirmation of Draft Minutes of ACCM 4 (3 December 2010)

Members accepted the Minutes of the fourth meeting of the ACCM as an accurate record of proceedings, subject to minor amendments as identified by Members.

Recommendation 5.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 4 (3 December 2010), as amended, are a true and accurate record of that meeting

3. Action Arising from Previous Meetings

3.1

ACCM discussed one matter under this agenda item. As this matter is still under consideration by the Committee, the information relating to this item will be withheld until the Committee has concluded its deliberations.

4. Guidelines on Levels and Kinds of Evidence to Support Claims

Nil items

5. Evaluation of New Substances

Nil items

6. Safety or Efficacy Reviews

6.1 *Dictamnus dasycarpus*

A TGA Officer introduced this item advising Members of possible safety concerns associated with the herbal species *Dictamnus dasycarpus*.

During the 1990s, multiple reports of liver damage associated with Chinese herb formulations (including *D. dasycarpus*) used to treat eczema and psoriasis were reported in Britain. In 2003 the Institute of Traditional Medicine (ITM) (Oregon, USA) reported a potential association with *D. dasycarpus* and rare, but serious, cases of liver reactions. Subsequently the herb was removed from formulations produced for the ITM. In 2010, the ITM released an alert after observing an increased number of literature reports of adverse liver reactions associated with *D. dasycarpus*.

A 2008 Korean report (English abstract) described four cases of toxic hepatitis that occurred several days after the patients consumed a decoction of *D. dasycarpus* root five to six times per day. The four

patients had a median age of 60 years, common symptoms of jaundice and general weakness, and stated that they had not consumed alcohol for at least 5 years. The report concluded that *D. dasycarpus* induced liver injury presenting with a benign course lasting less than 1 month after cessation of the causative agent.

An article published in *The Korean Journal of Hepatology* in 2010 (English abstract only) described a study of the medical records of 28 patients diagnosed between 2003 and 2008 with acute toxic hepatitis following ingestion of preparations of *D. dasycarpus* (no details on type of preparation provided). The biochemical pattern of liver injury was hepatocellular predominant and all patients recovered with supportive treatment.

There are currently 28 medicines included in the ARTG containing preparations of *D. dasycarpus*. There have been four adverse reactions reported in Australia between 2003 and 2007, two of which were liver related, one was kidney related and the last event was an exacerbation of psoriasis.

Members were asked to provide comment on the current status of *Dictamnus* species as eligible for use in Listed medicines.

Discussion

Regulatory status in Australia

The Chair clarified that there are currently two species of *Dictamnus* eligible for inclusion in Listed medicines, *D. dasycarpus* and *D. albus*. *D. dasycarpus* is included in 28 medicines, while *D. albus* is included in 2 medicines in the ARTG. While new ingredients approved for use in Listed medicines are evaluated, these two species were probably available in the Australian market when the ARTG was established, and therefore would have been 'grandfathered' in the list of permitted ingredients. Both herbal species are currently permitted for use in Listed medicines with no restrictions.

Traditional use

Members noted that *D. dasycarpus* is commonly used in China for skin conditions such as dermatitis and psoriasis. The herb had also been widely used in England in the 1990s as one ingredient in a formulation of Chinese herbs, which was reported to have substantial clinical benefit in the treatment of patients with eczema and psoriasis.

In Western herbal medicine *D. dasycarpus* is used as a cleansing herb to improve liver function for conditions such as hepatitis and skin conditions. A Member added that in 1934, the herb had been used in sitz/ steam baths in a Sydney hospital as an emmanagogue.

Adverse events in Australia

A TGA Officer advised that the product associated with one of the adverse events reported in Australia was found to be contaminated with aristolochic acid and the product had been recalled. A Member commented that aristolochic acid was associated with nephrotoxicity, not liver toxicity, and the adverse event in question was tubulointerstitial nephritis fibrosis.

International adverse events

It was noted that only the abstracts were available in English for the two clinical Korean papers (that reported adverse events for *D. dasycarpus*) and agreed a translation of these documents was required to ascertain the nature of the case histories; whether there was any concomitant factors; and determine if causality can be demonstrated.

Members commented that the exposure to the medicine is likely to be high in China, yet there have not been reports of adverse events in this country. Members questioned whether the issue of possible safety concerns for *D. dasycarpus* could be raised with the State Administration of Traditional Chinese Medicine (SATCM). A TGA Officer responded that it was possible this information could be sought under the Memorandum of Understanding between DoHA and SATCM.

Possible mechanism of toxicity

Members questioned what the mode of liver toxicity might be, noting that there was a lack of basic toxicity data, with no tests in animal models. A Member stated that the exact nature of liver damage would be unlikely to be shown in animal models, as an idiosyncratic adverse liver event might only occur in 1 in 10,000 or 1 in 1,000,000 people. It would be impossible to detect such an event in animal

studies.

Members noted that *D. dasycarpus* contains quinaline alkaloids which have been associated with liver damage. However, it is not possible to ascertain how highly concentrated the extracts (associated with the adverse events) are without more information in relation to the extraction ratio, solvents and plant part used. Further, the adverse events require a calculation of the equivalent dry herb to determine the dose. Members noted that 3 – 9 g has been stated as a traditional dose, which could equate to 700mg equivalent dry herb. A TGA Officer informed Members that the medicines included on the ARTG contain the herb in very small quantities. Another member stated that the herb was traditionally used in very small doses in China, in combination with a number of other herbs in the formulation.

It was noted that the herb had been around a long time, but adverse events had been reported in the last two decades, and questioned whether this could be the result of modern extraction techniques or indications. Members compared this to the case of kava, where modern ethanolic extractions were hepatotoxic, but the traditional water extractions were not associated with hepatotoxicity. However, it was noted that four adverse events reported for *D. dasycarpus* occurred in a rural setting where the preparation was a water decoction of the root, which, presumably, is the traditional preparation.

Epidemiology

Member noted that there had been approximately 30-40 cases reported of adverse liver events in over two decades of use. Considering the likely high amount of use, this was a relatively small number of events over a reasonably long period of time.

Consumer concerns

A Member stated that consumers may question why we are still allowing the herbal species to be used in Listed medicines, given the ITM information available in the public domain. It was considered this could be addressed on a case by case basis at this stage.

Outcome

Members noted the adverse events reported in the literature for *Dictamnus* species, but considered that, given the regulatory status and the widespread use of the species overseas, there does not appear to be a significant safety concern. The TGA was asked to maintain a watching brief at this stage.

7. Registration Applications

7.1

ACCM discussed one matter under this agenda item. As this matter is still under consideration by the Committee, the information relating to this item will be withheld until the Committee has concluded its deliberations.

8. Regulatory Reforms

Nil items

9. Adverse Drug Reactions associated with complementary medicines.

9.1 ADRs associated with complementary medicines from 1 November 2010 to 31 January 2011

ACCM noted the adverse events reported for complementary medicines from 1 November 2010 to 31 January 2011 however, due to time constraints individual cases were not discussed.

10. Matters Referred from within TGA

Nil

11. For information

11.1 Advisory Committee on Non-prescription medicines November 2010 minutes

Outcome

Members noted the Advisory Committee on Non-prescription medicines November 2010 minutes.

11.2 Medicines Safety Update No 6 bulletin 2010

Outcome

Members noted the Medicines Safety Update No 6 bulletin.

11.3 Medicines Safety Update No 1 bulletin 2011

Outcome

Members noted the Medicines Safety Update No 1 bulletin.

11.4 TGC Committee minutes

Members noted the August 2010 Therapeutic Goods Committee Minutes

12 Sponsor representations to ACCM

Nil items for consideration

13. Other Business

A Member requested that lengthy electronic agenda papers be presented with an index or table of contents. A TGA officer agreed that this could be done for future meetings.

14. Recommendation Record

Recommendation 5.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 4 (3 December 2010), as amended, are a true and accurate record of that meeting.

The Chair closed the meeting at 4:40pm.

Therapeutic Goods Administration

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