CMEC 24
Complementary Medicines Evaluation Committee

Extracted, Ratified Minutes
Twenty Fourth Meeting
1 December 2000
(Ratified at the 25th meeting, 2 February 2001)

Abbreviations:

ADEC Australian Drug Evaluation Committee
ADRAC Adverse Drug Reactions Advisory Committee
ADRU Adverse Drug Reactions Unit (of TGA)
ANZFA Australia New Zealand Food Authority
ARTG Australian Register of Therapeutic Goods
ASMI Australian Self Medication Industry
CHC Complementary Healthcare Council of Australia
CMEC Complementary Medicines Evaluation Committee
DSEB Drug Safety and Evaluation Branch
ELF Electronic Lodgement Facility
JHTF Joint Herbal Task Force
MEC Medicines Evaluation Committee
NDPSC National Drugs and Poisons Schedule Committee
OCM Office of Complementary Medicines
PBS Pharmaceutical Benefits Scheme
SUSDP Standard for the Uniform Scheduling of Drugs and Poisons
TGA Therapeutic Goods Administration
The twenty-fourth meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Conference Rooms, Sydney Airport, between 9:30 am and 2.50 pm on Friday 1 December 2000.

Members of CMEC present were:

    Prof David Roberts (Chair)
    Mr Nick Burgess
    Dr Roberta Chow
    Dr Colin Duke
    Dr Joachim Fluhrer
    Ms Val Johanson
    Prof Stephen Myers
    Mr Kevin Ryan
    Prof Tony Smith
    Prof Bill Webster
    Dr Heather Yeatman.

Present from the TGA were:

    Dr David Briggs
    Dr Fiona Cumming
    Dr Judy Cunningham.

1. Procedural Matters

1.1 Opening of Meeting

Professor Roberts as Chair opened the meeting at 9:30 am and welcomed members.

1.2 Apologies

There were no apologies from members for this meeting.

1.3 Conflict of Interest

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

2. Confirmation of Minutes of CMEC 23 (13 October 2000)

The minutes of the meeting of CMEC 23 were accepted as an accurate record of proceedings, subject to several minor amendments.
Recommendation 24.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 23), as amended, are a true and accurate record of that previous meeting.

3. **Guidelines on levels and kinds of evidence to support claims for therapeutic goods** (the ‘Guidelines’) and proposed warning statements for coded indications

At CMEC 23, members had developed a set of principles for determining the types of claims that would require warning statements. Using these principles, the TGA has reviewed the list of coded indications used in the Electronic Lodgement Facility (ELF) and has developed proposed warning statements for these indications.

*Present discussion:*

The Chairman asked members to identify indications where the proposed warning statements needed further consideration. Three coded indications were nominated - CALC2, SCAB and VAG2.

A member considered that the coded indication CALC2 (‘Source of calcium. A calcium supplement formulated to strengthen bone and tissue in growing and mature users.’) may not be informative and that the phrase “for children and older adults” may be preferable to “growing and mature users”. It was agreed that the indication should be altered to allow the optional use of the phrase “for children and older adults” as an alternative set of words.

The correctness of the indication “relief of scabies by topical application” (coded indication SCAB) was questioned. Scabies can only be truly relieved by treatment of the underlying infection. The statement “relief of the symptoms of scabies by topical application” is considered to more fully describe the action of topical non-prescription treatments. However given that the indication must be accompanied by the warning to seek medical advice if symptoms persist, members agreed that there was no pressing need to amend this coded indication.

The proposed warning statement to accompany the indication “for the symptomatic relief of vaginal itch” (VAG2) is “if symptoms persist consult your healthcare practitioner” (S). A member considered that persistent vaginal itch requires diagnosis of the underlying cause (e.g. by laboratory testing of swabs) and therefore requires a consultation with a medical practitioner. However members considered that a woman with persistent vaginal itch is likely to seek medical attention in any case given the unpleasant nature of the condition. In some cases, assistance from a complementary healthcare practitioner may be sought following diagnostic testing. For these reasons the majority of members considered that an amendment to the warning statement is unlikely to result in any different treatment outcome. Members agreed to retain the current wording of the proposed VAG2 warning statement.

Members next discussed a proposal to extend the warnings “adults only” or “not to be used in children under two years of age without medical advice” from cough and cold products to influenza/flu products. Members agreed that these warnings should apply equally to influenza/flu products.
Two proposed amendments to the warning statements for laxative products were discussed:

- Deletion of the words “increase fibre in the diet” from the warnings required for laxative products, as this statement is a lifestyle statement rather than a warning statement and may not be appropriate advice in cases where fibre supplements are being taken or where acute, severe constipation exists.

- Replacement of the laxative-specific warning statements “if digestive symptoms persist, seek medical advice” (DIG 1), “if symptoms persist, seek medical advice” (GEN) and “if symptoms persist, seek the advice of a healthcare professional” (GEN 2) with the general symptom coded warning statement “if symptoms persist consult your healthcare practitioner” (S).

Members supported the proposed amendments to the warning statements for laxative products.

Psoriasis products are currently required to carry the warning statement “Your healthcare professional will advise you whether this preparation is suitable for your condition” (PSOR). Members agreed it is not necessary to require this statement provided that products for psoriasis carried the general symptom warning statement (“if symptoms persist consult your healthcare practitioner”).

Members thanked the OCM for the amount and quality of work undertaken in applying CMEC’s principles to the development of warning statements for coded indications.

A general discussion then followed on whether the use of multiple label warning statements blunts the consumer impact of these statements. Specifically, members debated whether the use of the general warning to seek advice if symptoms persist could result in consumers failing to take notice of substance-specific label warnings, such as allergy warnings. Substance-specific warnings may be more important in terms of minimising product risk. Members were not aware of any research that would shed light on this matter. While accepting that over-use of warning statements may lessen their impact, it was considered that a committee such as CMEC has a duty to provide safety-related advice to consumers. Further, such advice could assist in the education of consumers about appropriate use of non-prescription medicines. Therefore, the label advice “if symptoms persist consult your healthcare practitioner”, should continue to be required.

Members made the following recommendation to the TGA:

**Recommendation 24.2**

CMEC recommended the adoption of a series of coded warning statements associated with coded indications used in the Electronic Lodgement Facility.
4. **Consultation strategy for proposed changes to the regulation of herbal medicinal substances**

Members were reminded that, at their last meeting, they had accepted the recommendations of the Working Party on Herbal Medicine Issues and requested that the Working Party’s report be reformatted into a consultation paper for distribution to stakeholders. A draft consultation paper has been prepared for members’ consideration.

**Present discussion**

The Chairman thanked the OCM secretariat for their work in developing the consultation strategy and document.

Members made a number of suggestions to assist with the editing of the draft document.

It was agreed that the issues identified in the draft consultation paper are complex. It would be worthwhile to acknowledge the complexity of the issues and to point out that the proposed solutions are only one approach, albeit a well-considered one, to this complexity. Respondents could be asked to identify instances where the suggested models for determining whether or not substances are herbal substances would not be able to be followed.

Because of the importance and complexity of the issues raised in the draft consultation paper, it is necessary to allow adequate time for consultation and for written comments to be received. Members therefore established a time-frame for the consultative process that they considered allows sufficient opportunity for broad consultation while recognising the need for timely finalisation of the process.

The initial stage of the consultation process should involve meetings between the Joint Industry TGA Herbal Task Force (JHTF) and some CMEC members. Following JHTF consultation, a revised consultation paper will be presented to CMEC members for consideration at the CMEC meeting in June. After this an industry workshop should be convened to facilitate open and constructive discussion of the issues raised. The consultation paper refined through the meetings with JHTF could be tabled at the industry workshop and released for general comment. The comment period should run through August and September. Final comments on the papers should be considered by CMEC at their meeting in October 2001.

5. **Action Arising from Previous Meetings**

CMEC considered a matter under this agenda item.
6. Evaluation of new substances

6.1 Conjugated linoleic acid 75%

Conjugated linoleic acid 75% (CLA 75%) is a substance produced from the saponification and purification of safflower oil in which the proportion of conjugated isomers of linoleic acid is approximately 75% of the total substance.

Present discussion:

The long-term toxicity of the range of isomers found in this substance was discussed. Some adverse effects may not become apparent until the substance has been consumed for some years, a longer time period than generally occurs in clinical trials. Further, members noted advice that only one of the major isomers in CLA 75% occurs naturally to any significant extent in the diet. Therefore it is not possible to rely on history of safe food use to support the safety of this substance, particularly the safety of trans-10, cis-12 octadecadienoic acid. Based on the information provided, there appears to be little evidence of long term clinical use of this isomer. The longest clinical trial of CLA 75% was conducted for only 6 months and full study details were not available. Members were reminded of the adverse effects of the long chain fatty acid erucic acid (cis-13-docosenoic acid) on heart muscle with long term consumption in high erucic acid rapeseed oil.

A member advised that there is a lot of current research interest in CLA generally and that some of this research has uncovered unexpected findings. For example, one study has found dose-related increases in liver retinol levels in female rats. Members noted that a study of weanling rats had found that CLA reduced bone formation in these growing animals. They also noted that a study of female mice had found that CLA might act as a peroxisome proliferator, although this has not been observed in rats or hamsters. In rodents, peroxisome proliferators are hepatocarcinogens, but this may be species specific.

The implications for humans of these studies are not clear but suggest the need for caution in allowing the use of this substance in listable therapeutic goods until more human data is available.

A study of Holstein cows has found that intra gastric administration of the trans-10, cis-12 isomer of CLA, at a rate of 10 g per day for four days, resulted in around a 40% reduction in milk fat concentration and yield. A similar effect in humans has been reported in the abstract of a study, although the full study was not available to the TGA. Inhibition of milk fat synthesis in women could impair the quality of human milk, which could have serious adverse effects on infant growth and development.

Possible therapeutic uses for CLA 75% were discussed and members noted that it is likely to be used in weight reduction/management programs. Consumers taking it for such reasons may be tempted to take high doses for long periods of time. If permitted for use in listable goods, CLA 75% is likely to be widely used given that it appears likely to have some effect on body fat and muscle levels.

Members made the following recommendation to the TGA:
Recommendation 24.3

CMEC recommends to the TGA that conjugated linoleic acid 75% is not suitable for use as an active or excipient ingredient in listable therapeutic goods as there is insufficient evidence of its safety for long-term human use, particularly that associated with the trans-10, cis-12 form of linoleic acid.

6.2 Calcium lactate gluconate

Members noted that Australians have already had significant exposure to calcium lactate gluconate as it was supplied in a popular Pharmaceutical Benefits Scheme medication until 1996 and remains on the ARTG. This medicine contained 5.23 g of calcium lactate gluconate per effervescent tablet. Since 1973 there have been only twelve reports to ADRAC where the medicine was the sole suspected cause of the adverse reactions. Three of these reports were of ‘certain’ causality and six of ‘probable’ causality. None of these twelve reports appeared to be of serious reactions. Therefore it appears that calcium lactate gluconate has a history of relatively safe supply to Australians.

The related substances from which calcium lactate gluconate is manufactured, calcium lactate and calcium gluconate, are currently permitted for use in listable therapeutic goods without any substance-specific conditions (e.g. dose restrictions).

A compositional guideline is not yet in place for this substance but will be developed following liaison between the TGA and the CHC.

Members made the following recommendation to the TGA:

Recommendation 24.4

CMEC recommends to the TGA that calcium lactate gluconate is suitable for use as an active ingredient in listable therapeutic goods.

7. Safety reviews

No matters were considered under this agenda item.

8. Registration applications

CMEC considered one matter under this agenda item.

Recommendation 24.5

CMEC recommended a product for registration.
9. Variation to a registered product

No matters were considered under this agenda item.

10. Matters referred from within the TGA

10.3 Report from the Adverse Drug Reactions Advisory Committee (248th meeting)

Members noted a summary of reports from the 248th meeting of ADRAC, held on 27 October 2000.

Present discussion:

Three reports had been received of interactions between St John’s Wort (Hypericum perforatum) and prescription medicines. One of these reports involved warfarin and the other two (‘possible’ causality) were apparent serotonin syndrome reactions with sertraline and fluvoxamine. Members were interested to note these reports as their occurrence had been predicted at the time of the review of label warning statements for St John’s Wort products.

A report of hypertension following use of a herbal preparation containing Panax ginseng and Ginkgo biloba, among other ingredients, had been received. A member advised that P. ginseng is generally contraindicated in cases of hypertension.

Finally, members discussed a report of seizures following use of evening primrose oil, the first time this has been reported in Australia. They recalled that in their 1999 review of the safety of evening primrose oil, the possibility of seizures in association with the use of this oil had been noted. These reports appear to largely involve patients also taking medication for schizophrenia.

Members discussed the merits of wider publication, via the medical literature, of complementary medicine adverse reaction reports. This could be of particular value in cases where certain reactions had been predicted and where these predictions were now being observed to occur. Apart from the resources that this would require, it was noted that it could be inappropriate to place too much emphasis on single case reports. Members were advised that it is ADRAC’s role to detect trends in adverse reactions, not to pursue individual reactions. ADRAC already has a bulletin that is used to alert practitioners to trends in adverse reactions.

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 24th meeting.
Item 2 Minutes of the 23rd meeting of CMEC

Recommendation 24.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 23, 13 October 2000), as amended, are a true and accurate record of that previous meeting.

Item 3 Guidelines on levels and kinds of evidence to support claims for therapeutic goods (‘Guidelines’) and proposed warning statements for coded indications

Recommendation 24.2

CMEC recommended the adoption of a series of coded warning statements associated with coded indications used in the Electronic Lodgement Facility.

Item 6.1 Conjugated linoleic acid 75%

Recommendation 24.3

CMEC recommends to the TGA that conjugated linoleic acid 75% is not suitable for use as an active or excipient ingredient in listable therapeutic goods as there is insufficient evidence of its long-term safety for human use, particularly that associated with the trans-10, cis-12 form of linoleic acid.

Item 6.2 Calcium lactate gluconate

Recommendation 24.4

CMEC recommends to the TGA that calcium lactate gluconate is suitable for use as an active ingredient in listable therapeutic goods.

Item 8 Registration applications

Recommendation 24.5

CMEC recommended a product for registration.

12. For Information

12.1 ADRAC database of suspected adverse reactions to drugs - explanatory notes

Members noted this item.
14. Other business

14.1 Aristolochic acid

A member advised that the European Agency for the Evaluation of Medicinal Products (EMEA) has recently released its final position paper on the risks associated with the use of herbal products containing Aristolochia species, and asked the TGA about the status of its investigation of therapeutic goods containing aristolochic acids.

A TGA officer advised that samples of all listed or registered products that contain herbs that may be confused with Aristolochia, have been tested for the presence of aristolochic acids. Eight products were found to contain aristolochic acids and have been subject to immediate recall and delisting. However, raw herbal material intended for extemporaneous dispensing may also inadvertently contain Aristolochia species. This type of material falls outside TGA’s jurisdiction, but the TGA has worked with the States and Territories, via the National Coordinating Committee on Therapeutic Goods, to alert them to potential problems. Meetings have also been held with Australian Customs to develop options for detecting Aristolochia arriving in Australia. The TGA has also contacted a range of complementary healthcare associations and medical practitioner groups, has placed material on the TGA website and has issued a press release on this matter.

The Chairman thanked members for their work during 2000, and wished them a Merry Christmas. The meeting closed at 2.50 pm on Friday 1 December 2000. The next meeting is to be held on Friday 2 February 2001.