

# **CMEC 22**

## **Complementary Medicines Evaluation Committee**

### **Extracted Ratified Minutes**

**(Ratified at CMEC 23, 13 October 2000)**

### **Twenty-second Meeting**

**25 August 2000**

#### **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
CMs	Complementary medicines
CMEC	Complementary Medicines Evaluation Committee
DSEB	Drug Safety and Evaluation Branch
ELF	Electronic Lodgement Facility
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
OCM	Office of Complementary Medicines
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration

# **CMEC 22**

## **Complementary Medicines Evaluation Committee**

### **Draft Minutes**

The twenty second meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Golden Wing Lounge, Sydney airport, between 9.30 am and 4.45 pm on Friday 25 August 2000.

Members of CMEC present were:

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

Present from the TGA were:

Dr Susan Alder  
Dr David Briggs  
Dr Fiona Cumming  
Dr John Hall.

### **1. Procedural Matters**

#### **1.1 Opening of Meeting**

Professor Roberts as Chair opened the meeting at 9.30 and welcomed members. Professor Roberts welcomed Dr Susan Alder of TGA who was observing the meeting.

#### **1.2 Apologies**

There were no apologies.

#### **1.3 Conflict of Interest**

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

## **2. Confirmation of Minutes of CMEC 21 (6,7 July 2000)**

### **Recommendation 22.1**

**CMEC confirms that the draft Minutes of its previous meeting (CMEC 21) as amended at the present meeting be considered a true and accurate record of that meeting.**

#### **2.1 St Johns Wort Information Sheet**

Members considered a document titled “Information For Consumers Taking St John’s Wort”.

The Information Sheet was considered acceptable with minor changes.

## **3. Substantiation of Claims – Levels of Evidence**

A TGA officer gave an overview of numbers and types of claims to go before the “Advisory Group”. This group had been set up in February 2000 to provide advice to sponsors on how to use the “Draft Guidelines for Levels and Kinds of Evidence to Support Claims for Therapeutic Goods” (The Guidelines) in designing and substantiating therapeutic claims proposed for their products.

It was reported that the Advisory Group had looked at over 400 claims, around 230 of which were new claims unable to be made under the previous arrangements. It was reported that of the over 400 claims, around 80 were deemed to be high level claims requiring registration of the product. Only 12 claims were considered unacceptable in that they were unsupported from the level and type of evidence provided and therefore potentially misleading.

A revised version of the Guidelines, included with the agenda papers, incorporated all of the changes since the previous CMEC meeting. The TGA officer indicated that endorsement by CMEC of the revised document would mean approval to undertake a final round of consultation with stakeholders. If acceptable to CMEC, TGA would go back to stakeholders for final comments and then, after consideration of comments, the document would be published.

The TGA officer explained that the most recent edits to the Guidelines had rendered it more user-friendly and had taken account of industry concerns over the loss of certain ‘high level’ claims by allowing them within what are known as ‘coded indications’. The TGA officer also explained that the intention was to make the document as clear and comprehensible as possible and this had meant the inclusion of some further explanatory text. The draft before the Members at the meeting incorporated a short executive summary for quick reference. The Chair called for suggestions as to how the document might be improved and a series of mainly minor amendments to the Guidelines was suggested by Members for incorporation into the final draft of the Guideline for industry consultation and future application by stakeholders.

Members endorsed this version of the Guidelines as thus amended and congratulated the TGA on the quality of the efforts made to produce the present document.

#### **4. Report of the CMEC Working Party on Herbal Medicine Issues**

Members considered the Final Report of the CMEC Working Party on Herbal Medicine Issues. A TGA officer explained that CMEC's endorsement of this Report was being sought and that this would form the basis for consultation and discussions with stakeholders, the results of which would be considered by CMEC before the Committee finalised its report to the TGA.

The Chair congratulated the members of the Working Party for progressing this issue to the point where a consolidated Report was now available. One member provided an overview of the rationale behind each of the recommendations in the Report. Another provided an overview of the flow chart for determining the suitability of a herbal substance for use as a component of Listable medicines. It was explained that the purpose of the chart is to assist in determining when the degree of processing or refinement undergone by a herbal material is such that the product can no longer automatically be considered to be the same herbal material as is permitted for use in Listable medicines. The development and use of a rating scale for various refinement steps undergone by a herb from the raw state was also explained to Members. Members agreed the model, which had been developed using the flow chart and the rating scale, would provide a useful basis for stakeholder consultation.

Members noted a number of changes in the documentation from the information provided in previous reports from the Working Party to CMEC.

Members approved the general approach taken by the Working Party and reflected in the Final Report. In the time available the Members were able to endorse some of the recommendations. It was agreed to give priority at the next meeting to considering the full report.

#### **5. Action Arising from Previous Meetings**

##### **5.1 CMEC 20 Meeting**

###### **5.1.1 Phenylalanine**

At the last meeting (CMEC 21), Members discussed the safety of L-phenylalanine, which is currently permitted as an active ingredient in listable therapeutic goods. The review of the safety of L-, DL- and D-phenylalanine has been undertaken as part of a commitment by the TGA to industry to review the safety of a number of complementary medicine substances currently permitted for use only in registered goods. Under the Therapeutic Goods Regulations, DL- and D-phenylalanine (but not L-phenylalanine) are specifically excluded from use in listable goods.

Discussion at the previous meeting (CMEC 21) had focussed on the risks to the foetus associated with ingestion of supplemental phenylalanine during pregnancy by women who are heterozygous for phenylketonuria (PKU). Members agreed to defer making a decision on the suitability of L-, DL- and D-phenylalanine for use in listable therapeutic goods until it has been able to consider in more detail a number of matters relating to the safety of these

substances, and of the artificial sweetener aspartame, during pregnancy. One Member undertook to review some of the papers cited in the evaluation report.

The Member tabled a paper showing the blood levels of phenylalanine under various conditions including;

- in normal people (around 60  $\mu\text{mol/L}$ );
- in phenylketonurics (around 1200  $\mu\text{mol/L}$ );
- following ingestion, by normal people, of differing doses of aspartame (150 – 360  $\mu\text{mol/L}$  after 100mg/kg aspartame and around 490  $\mu\text{mol/L}$  after 200 mg/kg of aspartame);
- in heterozygous individuals (from 60 – 120  $\mu\text{mol/L}$ );
- in heterozygous individuals after phenylalanine loading with 100 mg aspartame (300 – 600  $\mu\text{mol/L}$ ); and
- maternal levels in pregnancy considered to be associated with mental retardation (greater than 400  $\mu\text{mol/L}$ ).

Members discussed the implications of this data for the potential manner in which L-phenylalanine might be used as a Listable medicine. Discussion included consideration of the following:

- the need to avoid sustained blood levels of L-phenylalanine above the 400  $\mu\text{mol/L}$  which are considered to be associated with untoward effects on the foetus;
- concern that heterozygous women might become pregnant and not realise the need to minimise phenylalanine intake;
- that there is considerable variation in the population as to the rate and capacity to metabolise L-phenylalanine; and
- that dietary sources of L-phenylalanine become an issue given that L-phenylalanine is a normal component in meat and other foods

Members considered that the risk to pregnant women and their offspring was extremely difficult to quantitate. At the levels currently used in Listable medicines (commonly marketed dosage forms contain up to 500 mg) that risk appeared to be minor even when contribution from dietary sources is taken into consideration. Members agreed that L-phenylalanine was suitable to continue to be used in Listable medicines, but there was general agreement that it would be reasonable to recommend an appropriate labelling warning as to the potential risk to pregnant women. The potential impact on the industry of the imposition of a labelling requirement was also discussed.

The possibility of defining a daily dose limit below which any labelling was not required was then considered. Members agreed that products for which the recommended daily dose did not exceed 500 mg should not require a pregnancy warning.

The following recommendation was made to the TGA:

### **Recommendation 22.2**

**That the suitability of L-phenylalanine as an active ingredient in listable therapeutic goods is confirmed subject to a labelling warning “Do not use if pregnant or likely to become pregnant” where the recommended daily dose exceeds 500mg.**

Members then briefly considered the regulatory status of the D- and D,L- isomers of phenylalanine. It was noted that there was general lack of evidence pertaining to the safety and efficacy of these isomers and so Members were reluctant to make any recommendation about their safety at this stage. It was agreed to maintain a watching brief on these isomers and to seek further data pertaining to their safety and efficacy as it becomes available.

## **6. Evaluation of new substances**

### **6.1 *Santalum spicatum***

CMEC was being asked to consider whether or not *Santalum spicatum* (Australian sandalwood) oil is suitable for use as an active ingredient in listable therapeutic goods.

A TGA officer introduced this item, mentioning the method of production of the oil and comparing its chemical composition with the more common East Indian sandalwood oil, *Santalum album*. He indicated that safety considerations had relied both on the history of use of the East Indian product and on an assessment of the differences in the composition of *Santalum spicatum* and *Santalum album*, and the toxicological and other safety implications of these differences.

Members noted that while the data provided on the history of use of the East Indian oil provided a good level of supporting data on the safety of the Australian oil, they were not convinced the sum of the available data was sufficient to support the oral use of the product. They were prepared to support topical and inhalational use given that it was unlikely that such use would generate appreciable systemic concentrations, and they recommended that the following advice be provided to the TGA:

### **Recommendation 22.3**

**That *Santalum spicatum* oil is suitable for use in listable therapeutic goods for topical or inhalational use but not oral use.**

The reasons for this decision were as follows:

- There is a reasonable level of chemical similarity between the oils of *Santalum spicatum* and *Santalum album*; the latter appears to have a safe history of topical use.
- A number of products containing *Santalum album* oil are listed on the Australian Register of Therapeutic Goods (ARTG) for topical and inhalational use.
- There has been previous limited medical/pharmaceutical use of *Santalum spicatum* oil, without known adverse effects.
- Registered or listed products containing *S. album* oil are not approved for oral administration. If a qualitative parallel is drawn between these two oils, the same condition should apply also to *S. spicatum* oil, and it should not be approved for oral administration; similarly, it should be approved for topical and inhalational administration.
- Several sources in the literature reported that *S. album* oil may produce kidney damage when ingested.

## 6.2 *Backhousia citriodora*

CMEC was asked to consider whether the leaf oil of *Backhousia citriodora* (lemon myrtle) is suitable for use as an active ingredient at a concentration not exceeding 1% w/w in listable therapeutic goods

A TGA officer introduced this item pointing out that the proposed use was as an antiseptic for use in pimples and acne. He indicated that the product was about 98% citral and that therefore safety considerations had centred around the safety of citral and took account of the fact that citral was included in a wide variety of products, including non-therapeutic products.

Members considered the following issues in regard to the safety of *Backhousia citriodora*:

- the existing exposure of the population to the active ingredient citral given that it is widely used in the household, cosmetic and food industries and the apparent lack of known adverse reactions associated with such exposure; and
- the paucity of other important data on its metabolism which might inform an assessment of the significance to humans of the physiological alterations induced by topical citral in rats;
- that any decision on *Backhousia citriodora* should be consistent with other decisions based on a less than complete set of safety and pharmacokinetic data; and
- that topical administration of *Backhousia citriodora* presented a potential risk but that this risk was probably small.

Members recognised that the additional data needed to be more certain about any safety risk posed by *Backhousia citriodora* was unlikely to exist and agreed, on the balance of the totality of evidence available, subject to the inclusion of label warnings, to make the following recommendation to the TGA:

### **Recommendation 22.4**

**That *Backhousia citriodora* leaf oil at a concentration not exceeding 1% (w/w) is suitable for use in listable therapeutic goods for topical use.**

## 10. Matters referred from within the TGA

### **10.6 Reports from the 245<sup>th</sup> and 246<sup>th</sup> meetings of the Adverse Drug Reactions Advisory Committee (ADRAC) and of Special CMEC/ADRAC Meeting**

A Special Meeting of representatives of both CMEC and of the ADRAC had been held the previous day (24 August 2000) and Members were provided with a brief overview of that meeting. At that meeting, the need to encourage greater dialogue between the two committees with respect to adverse reaction reports had been discussed.

The Chair tabled the most recent report to CMEC from ADRAC (245<sup>th</sup> and 246<sup>th</sup> Meetings. A CMEC member, who is also a member of ADRAC, lead the discussion on these ADRAC reports.

## **Recommendation 22.5**

**The CMEC would provide comment to the Adverse Drug Reactions Advisory Committee (ADRAC) on reports from the ADRAC.**

## **11. Recommendation record**

CMEC members adopted the following as a summary of the recommendations made at its 22nd meeting.

### **Item 2 Confirmation of Draft Minutes of CMEC 21**

#### Recommendation 22.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 21) as amended at the present meeting be considered a true and accurate record of that previous meeting.

### **Item 5.1 Action Arising From Previous Meeting - Phenylalanine**

#### Recommendation 22.2

That the suitability of L-phenylalanine as an active ingredient in listable therapeutic goods is confirmed subject to a labelling warning “Do not use if pregnant or likely to become pregnant” where the recommended daily dose exceeds 500mg.

### **Item 6.1 *Santalum spicatum***

#### Recommendation 22.3

That *Santalum spicatum* oil is suitable for use in listable therapeutic goods for topical or inhalational use but not oral use.

### **Item 6.2 *Backhousia citriodora***

#### Recommendation 22.4

That *Backhousia citriodora* leaf oil at a concentration not exceeding 1% (w/w) is suitable for use in listable therapeutic goods for topical use.



**Item 10.6 Consideration of Reports from the Adverse Drug Reactions Advisory Committee**

Recommendation 22.5

That CMEC would provide comment to the Adverse Drug Reactions Advisory Committee (ADRAC) on reports from the ADRAC.

The meeting closed at 4:45 pm on Friday 25 August 2000. The next meeting is to be held on Friday 13 October 2000.