CMEC 25

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Twenty Fifth Meeting
2 February 2001
(ratified at the 26th meeting of CMEC, 23 March 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-fifth meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Conference Rooms, Sydney Airport, between 9:30 am and 4.00 pm on Friday 2 February 2001.

Members of CMEC present were:

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

Present from the TGA were:

- Dr Susan Alder
- 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 to the first meeting of the new year.

1.2 **Apologies**

There were no apologies 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 24 (1 December 2000)**

The minutes of the meeting of CMEC 24 were accepted as an accurate record of proceedings, subject to minor amendments.
Recommendation 25.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 24), 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’)

Following CMEC’s 23rd meeting, the Guidelines were amended and publicly released in November 2000. Stakeholders were invited to comment on this version of the Guidelines. A number of submissions were received. The comment received has been included in this agenda item for CMEC consideration.

Present discussion:

A number of aspects of the Guidelines were discussed, as summarised below.

General value, content and application of the Guidelines

Members noted that some respondents considered that the Guidelines are somewhat long, complex and scientifically focussed, while others commented that they are generally acceptable.

Members discussed ways to simplify the document and considered that it would be helpful if the section on traditional claims were placed before the section on scientific claims. Once there is substantial agreement on the revised version of the Guidelines, the document will be professionally edited. One area that could particularly benefit from editing is the Executive Summary, which was felt to be too long.

The CHC is preparing a simplified version of the Guidelines to assist advertisers and marketers. When this document is available for CMEC consideration, it may be helpful for members of the CMEC Working Group on Levels of Evidence to meet with industry representatives.

Members suggested that the Guidelines could also incorporate a glossary of terms such as ‘randomised’ and ‘controlled’.

Members were reminded that, in the past, the option of generating a list of acceptable claims and the evidence to support these claims had been discussed. While it was noted that it would be helpful to industry if even a small list of acceptable claims and evidence were to be developed by the TGA or industry and vetted by CMEC, it would be a huge task to develop even this small list, particularly given that complementary medicine substances are often not clearly defined and may vary widely in chemical composition. Indeed, it was to avoid this very situation that the Guidelines were developed, so that sponsors were given a set of principles on which to make their own decisions about claims and evidence. Members agreed that it was not appropriate for CMEC to develop a list of acceptable claims and the evidence to support these claims.

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It appears that there is a need for education in the use of the Guidelines. For example, sponsors could be assisted by an education program on how to identify and use traditional evidence sources. The Drug Safety and Evaluation Branch of TGA had undertaken a similar education process when principles were developed for the use of literature-based submissions for prescription drugs.

### Evidence for scientific claims

For Table 1, members clarified that the evidence requirement for high level scientific claims (data from at least two independent trials), refers to trials that are independent of each other, that is, different patient groups are used. In a multicentre trial, data from each centre does not constitute an independent trial. This requirement does not imply that the trials must be conducted by someone who is independent of the sponsor. It was agreed to amend the wording of this requirement to state “It is preferable to have data from at least two trials independent of each other”.

For claims based on scientific evidence it was agreed to retain the word ‘quantifiable’ in the definition of scientific evidence. A respondent had queried whether or not texts, monographs and pharmacopoeia contribute to ‘quantifiable’ scientific evidence. Members noted that this will depend on the level of the claim (medium or general level claims only) and on the content of these references.

Members confirmed that evidence from suitable pharmacopoeia or monographs are sufficient for a general level claim based on scientific evidence.

### Evidence to support traditional claims and the wording of traditional claims

Concerns were expressed with the section of the Guidelines that relates to traditional claims. One of the areas of concern was with identifying the tradition on which a claim is to be based. Some evidence sources (e.g. Commission E monographs) identify that a medicine is used traditionally for certain indications but do not identify the source of the tradition (e.g. Chinese medicine, Ayurvedic medicine). Members considered that there will almost always be an evidence source that does identify the tradition on which a claim is based (for example, the Napralert database cites original references from 1650 onwards). Further, it appears that in the US, where the traditional modality does not have to be identified, there has been a plethora of doubtful claims that substances have a traditional medicinal use. Consumers are not greatly assisted by such claims, particularly if they are interested in buying a medicine as part of following a particular therapeutic modality. Finally, if a sponsor is not fully informed of the traditional basis for a claim, it is likely that the claim will be inaccurate. For these reasons it was agreed that the current requirement to identify the specific tradition of use should be retained.

The intent of the Guidelines in relation to traditional medicines is not to regulate the formulation of such medicines, but to require that claims based on traditional evidence take into account the traditional manner of use of such medicines. If a substance traditionally used in Chinese medicine, for example, is used in a medicine containing a range of vitamins, the medicinal substance is now being used outside its traditional paradigm. Therefore any claims made for that medicinal substance should make clear that it is not being used in a traditional manner.
Products carrying medium level, traditional claims are required to use the label statement “This (tradition) medicine has been used for (indication). This claim is based on traditional use.” The reason for this wording was to indicate clearly to consumers that a product claiming to reduce risk of a disease, to relieve symptoms of a disease or to assist in the management of a disease was not making this claim based on scientific evidence. However members considered, after some debate, that the subtleties of this wording may not be evident to consumers. The required wording consumes considerable extra label space compared to the required wording for general level traditional claims. Members agreed that products making medium level, traditional claims (including claims for homoeopathic medicines) can carry the same label statement as for those making general level claims (“This [tradition] medicine has been traditionally used for [indication].”).

Claims for homoeopathic medicines

In Table 1, which refers to claims based on scientific evidence, it was agreed to retain reference to well-designed, controlled homoeopathic provings rather than to homoeopathic repertories as the majority of material contained in homoeopathic repertories comes from provings. However members agreed that on page 18 of the Guidelines, the sentence “Providing that a new substance is prepared according to principles described in TGA-approved homoeopathic Materia Medica and Repertory ...” should be amended to refer to homoeopathic pharmacopoeia rather than Materia Medica and Repertories, as it is the pharmacopoeia that describe preparation methods.

Members noted an extensive submission on claims for homoeopathic medicines from a sponsor who manufactures homoeopathic medicines based on the anthroposophical paradigm of homoeopathy. This paradigm in part allows for homoeopathic medicine treatment of named conditions rather than symptom pictures, as is the case with classical homoeopathy. Anthroposophical medicine has been practised for over a century and would meet the definition of a traditional technique (more than three generations of use) in its own right. It was agreed that, in Table 5 relating to claims for homoeopathic medicines, reference to symptom pictures should be retained, recognising that anthroposophical medicines could make claims for named conditions under the general requirements for traditional medicines.

List of indicative sources of supporting evidence

There appears to be continuing confusion with the purpose of the list of indicative sources of evidence which may be used to support claims (Attachment 2 of the Guidelines). Some sponsors appear to still consider, incorrectly, that the list is proscriptive and therefore that they cannot use an evidence source that is not named in the list. Others have requested information on the evidence sources that were considered unsuitable for inclusion. While members understood that this information would be helpful to sponsors, they considered that publication of a list of ‘unacceptable’ evidence sources has the potential to be misleading.

Members were informed that the Advisory Group, established by the TGA to examine proposed label claims, had developed a set of principles to assist sponsors assess the adequacy of an evidence source. A respondent had also submitted a list of principles for judging the suitability of monographs; this list merits further development.

Members agreed that the following texts should be included in the list of indicative evidence sources: the Anthroposophical Medicine Commission C monographs, the Lawrence Review
of Natural Products Monograph Series and the German, French and US Homoeopathic Pharmacopoeia.

Members agreed that, in order to simplify the Guidelines document and to remove a source of confusion for sponsors, the list of indicative sources should be removed from the Guidelines. Instead, a list could be incorporated into the simplified version the CHC is developing.

Other matters

In the third paragraph of page 12, the last sentence should be deleted and replaced with “Some registrable therapeutic goods may require special approval to advertise. TGACC is responsible for such recommendations”, to clarify that this special approval only relates to registered goods.

Members agreed that the sentence “They must be consistent with the recorded use on the Australian Register of Therapeutic Goods in relation to that product” should be deleted from the second principle relating to claims (page 12 of the Guidelines). The Guidelines are intended to assist sponsors to formulate claims prior to the listing or registration of a product, in which case the product would not already be included in the ARTG.

The wording of the label warning statement that must be used in association with claims for symptomatic relief is “If symptoms persist consult your healthcare practitioner”. Members considered a request to amend this wording to allow optional use of the phrase “healthcare professional”. However members did not accept this amendment as they considered that advice should be sought from someone who is actually practising in a healthcare modality, rather than simply being qualified (i.e. a professional) but not practising.

The coded indication, MUSC3 (“Aids or assists in the prevention of muscle cramps and spasms”) was reinstated in the list of acceptable coded indications. It was also agreed to retain the coded indication MUSC13 (“Prevention of cramps/muscular cramps or sprains”).

Members noted that the changes recommended at this meeting will be incorporated into the Guidelines. The amended Guidelines will be distributed again to stakeholders, together with an acknowledgment that the CHC is preparing a simplified version of the Guidelines. Once the simplified version is available, members of the CMEC Working Group could meet with industry representatives to discuss future developments.

Members made the following recommendation to the TGA:

**Recommendation 25.2**

CMEC recommended the adoption of a number of minor amendments to the Guidelines (November 2000 version). CMEC also looks forward to receiving a draft, simplified version of the Guidelines, being developed by the Complementary Healthcare Council of Australia for industry, to facilitate future consideration of this matter.
4. **Consultation strategy for proposed changes to the regulation of herbal medicinal substances**

At CMEC 24 members considered a draft stakeholder consultation paper on the appropriate regulation of herbal substances and recommended some editorial changes to the paper. This draft paper had been developed as an outcome of the CMEC Working Party on Herbal Medicines. The revised paper was presented to a meeting of the Joint TGA Industry Herbal Task Force (JHTF), held on Thursday 1 February 2001 and CMEC is working with the JHTF to finalise the paper for consultation.

*Present discussion:*

The Chairman thanked the OCM secretariat for their work in redrafting the consultation paper under a very tight timetable, and for the quality of the redrafted paper. He also thanked members who had provided comments to assist with the editing of the paper.

Another meeting of the JHTF, including some members of CMEC, is to be held in late April 2001. Comments on the paper will be discussed at this meeting and collated comments referred to CMEC at its June 2001 meeting.

5. **Action Arising from Previous Meetings**

5.1 **CMEC 22 Meeting (August 2000)**

5.1.1 **Phenylalanine – proposed label warning statement**

Members were reminded of their decision at their 22nd meeting (August 2000) to recommend to the TGA that all medicines containing L-phenylalanine as an active ingredient should carry the following label warning statement when the recommended daily dose of L-phenylalanine exceeds 500 mg:

> Do not use if pregnant or likely to become pregnant.

The label warning was recommended to reduce the likelihood of damage to the fetuses of women who are heterozygous for phenylketonuria. These women may be susceptible to elevated blood phenylalanine levels if a substantial amount of supplemental phenylalanine is consumed.

*Present discussion:*

Members noted that the TGA had adequately responded to the issues raised in the two submissions that it had received following a period of stakeholder comment on the above recommendation. They also noted that no further comment had been received from stakeholders after the TGA had supplied them with additional information. Given that no substantial issues have been raised in relation to the warning, the TGA will amend the Therapeutic Goods Regulations to require the above statement.
Recommendation 25.4

CMEC noted that no substantial issues had been raised during stakeholder comment on the proposed label warning statement (“Do not use if pregnant or likely to become pregnant”) for products containing more than 500 mg L-phenylalanine per recommended daily dose. Members noted that the Therapeutic Goods Regulations will be amended to require the use of this warning statement on listed medicines.

6. Evaluation of new substances

6.1 Conjugated linoleic acid 60%

Conjugated linoleic acid 60% (CLA 60%) is a substance produced following the saponification and purification of sunflower oil. Two particular conjugated isomers of linoleic acid predominate and the proportion of conjugated isomers of linoleic acid is approximately 60% of the total substance.

Present discussion:

Members were advised that CLA 60% is not the same substance as CLA 75%, which was considered at CMEC 24 (December 2000). Nevertheless the two substances are of similar chemical composition, differing largely in the total content of conjugated isomers of linoleic acid.

CMEC recommended in December 2000 that CLA 75% is not suitable for use as a listable substance as there is a lack of evidence of long term safety for human use, particularly of the trans-10, cis-12 isomer. In making this recommendation the following issues related to the safety of CLA 75% had been highlighted:

- 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 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 dietary use to support the safety of this substance, particularly the safety of trans-10, cis-12 octadecadienoic acid. Based on the information provided to the TGA, there appears to be little evidence of long-term clinical use of this isomer. The longest clinical trial of CLA 75% reported to the TGA 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.

- There is a lot of current research interest in CLA generally and 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 are 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.

The only additional information in the present application (CLA 60%) that relates to safety for human use is a study of only 17 females for a total of 64 days. There is no additional evidence of the long-term safety of CLA for human use.

Members made the following recommendation to the TGA:

**Recommendation 25.5**

CMEC recommends to the TGA that conjugated linoleic acid 60% is not suitable for use as an active or excipient ingredient in listable therapeutic goods as there is insufficient evidence to support its long-term safety for human use, particularly that associated with the trans-10, cis-12 form of linoleic acid.

**6.2 Sugar cane wax alcohols**

A TGA officer introduced this item and explained that sugar cane wax alcohols (SCWA) are produced following saponification of a waxy extract of *Saccharum officinarum*, L. The substance does not fit the definition of a herbal substance under the Therapeutic Goods Regulations.

**Present discussion:**

Discussion focussed on the similarity of SCWA to the related, more highly purified, substance policosanol. Impurities present in SCWA are likely to also be present in policosanol, albeit at a slightly lower level. Because of this compositional similarity, members judged that the considerable body of published data available to support the safety of policosanol is applicable to an assessment of the safety of SCWA.

In support of the suitability for use of SCWA in listable therapeutic goods, CMEC noted the following:

- Clinical trials and continuing post-market vigilance of SCWA support its low risk nature, even among older adults with pre-existing illness or disease risk factors who are taking other medications. However clinical trials have been restricted to a daily
dose of up to 12 mg SCWA. Safety of higher doses in humans has not been established.

- The safety of the closely related substance policosanol has been demonstrated for up to 3 – 5 years of usage.
- Animal studies have not identified any issues likely to be of concern for human use of SCWA, other than the potential for placental transfer of components of SCWA.
- There is a documented history of use of SCWA as a food supplement in Cuba, and of policosanol as a medicine in a range of South American and Eastern European countries.
- There is some dietary consumption of long chain aliphatic alcohols although it is not possible to quantify intake.

Members considered that SCWA is suitable for use as an active ingredient in listable therapeutic goods, but considered that it would be prudent to place two restrictions on its use:

- a daily dose limit of 12 mg, in line with doses used in clinical trials. This would also have the effect of limiting exposure to any impurities; and
- a label advisory statement that the substance is not suitable for use during pregnancy and lactation, as there may be some placental transfer of the substance. However members noted that a rat peri- and post-natal toxicity study of policosanol did not identify any adverse outcomes for the offspring of mothers fed policosanol.

Members made the following recommendation to the TGA:

**Recommendation 25.6**

CMEC recommends to the TGA that ‘sugar cane wax alcohols’ is suitable for use as an active ingredient in listable therapeutic goods, provided that the recommended daily dose of the substance does not exceed 12 mg, and that goods containing the substance carry the following label advisory statement:

“Not recommended for use by pregnant and lactating women” (or words to that effect)

### 6.3 Thiamine phosphoric acid ester chloride

Thiamine phosphoric acid ester chloride (thiamine PAEC) is the monophosphate ester of thiamine. It has the molecular formula of C₁₂H₁₈ClN₄O₄PS (anhydrous) and a molecular weight of 380.8 (anhydrous) and 416.8 (dihydrate).

**Present discussion:**

Members noted the following matters in support of the safety of thiamine PAEC:
• Thiamine PAEC has a history of safe use as both a food additive and as an active ingredient in registered, non-prescription medicines.
• It appears to be bioavailable and metabolically interconvertible with free thiamine and the active co-enzyme form of thiamine.
• Thiamine nitrate and thiamine hydrochloride are already permitted as active ingredients in listable therapeutic goods, without any substance-specific restrictions on their use.
• It is one of the phosphate esters of thiamine that are naturally present in the diet.

Members made the following recommendation to the TGA:

**Recommendation 25.7**

CMEC recommends to the TGA that ‘thiamine phosphoric acid ester chloride’ is suitable for use as an active ingredient in listable therapeutic goods, without any substance-specific restrictions on its use.

6.5  **(S)-S-adenosyl-L-methionine**

SAMe is synthesised in the cytosol of every mammalian cell and is central to the processes of transmethylation, transulfuration and polyamine synthesis. A normal adult synthesises approximately 8 g SAMe per day, mainly in the liver.

*Present discussion:*

Members noted advice that SAMe may be able to encourage ‘switching’ from depressive to manic states in bipolar patients. However use of selective serotonin reuptake inhibitors (SSRIs) is also known to be associated with manic reactions as a rare side effect. Listed medicines containing SAMe would not, of course, be able to make claims about depression.

SAMe appears to have a safe history of use in other countries, including in Europe and the United States, although this safe history of use appears to be associated with the tosylate (para-toluene sulfonate) and sulfate salts rather than the butane disulfonate. Clinical trials of SAMe, using enteric coated tablets, have reported minor adverse reactions only. The form of SAMe used in these trials has not always been identified, although certainly the tosylate and butane disulfonate salts have been used in some trials.

SAMe appears to be produced mainly by fermentation of yeast cultures in the presence of L-methionine, followed by extraction of the SAMe that accumulates in the yeast cells. Very little information was provided on the production of SAMe by other methods, including the use of recombinant organisms or synthesis using potentially hazardous reagents. In the absence of information to demonstrate the safety of non-fermentative processes, such processes cannot be recommended in relation to listable goods.

In some fermentative processes, SAMe is precipitated using picrolonic acid, which has been identified as being mutagenic and for which a no adverse effect level has not been set. Therefore, to reduce the risk associated with the use of SAMe in listable therapeutic goods, a requirement should be established that picrolonic acid must not be used in SAMe production.
If SAMe becomes available in listed medicines, adverse reactions associated with it should be monitored, particularly in relation to some of the rare adverse reactions observed with SSRIs, such as ‘switching’ from depressive to manic states.

Members made the following recommendation to the TGA:

**Recommendation 25.9**

CMEC recommends to the TGA that (S)-S-adenosyl-L-methionine is suitable for use as an active ingredient in listable therapeutic goods, provided that the following conditions are met:

- only the p-toluene sulfonate and sulfate salts (or a mixture thereof) are used;
- these substances are only produced by fermentative processes; and
- picrolonic acid is not used in the manufacturing process.

### 6.6 Lycopene

A TGA officer introduced this item and stressed that lycopene is a labile molecule, highly susceptible to oxidation. While these double bonds are predominantly in the all-trans configuration in nature, isomerisation occurs during processing, such as during heating while cooking tomatoes. Synthetic lycopene contains approximately 70% all-trans lycopene but the isomeric distribution within synthetic lycopene is similar to the distribution found in cooked tomatoes. Commercially, lycopene is stabilised to minimise degradation.

**Present discussion:**

There are a considerable number of products listed in the ARTG that contain tomato extract for which an equivalent quantity of lycopene has been declared. The maximum lycopene content per dose of these products is 6 mg. The Australian Adverse Drug Reactions database holds no reports of adverse reactions associated with these products. The US Special Nutritionals Adverse Event Monitoring System also has no reports of adverse reactions associated with lycopene supplements in the US.

Lycopene is a normal part of the Australian diet. There is no evidence that synthesised or highly purified lycopene would have adverse reactions different from lycopene normally found in foods. Lycopenemia has occurred in association with extreme dietary intake of tomato products over long periods of time, but has been shown in animal and human studies to be reversible.

*In vitro* and *in vivo* animal toxicity studies with both natural and synthetic lycopene have not shown specific toxic effects. Reproduction and teratologic studies using the oral route have been uneventful. Mutagenicity *in vitro* of unstabilised lycopene that had been exposed to light and air was shown in two bacterial strains out of seven. However in another study, formulated, stabilised lycopene did not show any mutagenicity *in vitro* when exposed to the same conditions of light and air as the unstabilised lycopene. In any case, mutagenicity *in vitro* does not necessarily equate with mutagenicity *in vivo*. Concerns about mutagenic potential of stored lycopene could be dealt with by requiring lycopene used in listed therapeutic goods to be stabilised to minimise degradation.
Members made the following unanimous recommendation to the TGA:

**Recommendation 25.10**

CMEC recommends to the TGA that lycopene is suitable for use as an active ingredient in listable therapeutic goods, provided that it is stabilised to minimise degradation.

A member noted that a recent review article of the epidemiologic literature on tomatoes, lycopene and cancer\(^1\), provided with the agenda papers, had concluded that it is premature to recommend pharmacologic doses of lycopene for any health benefit. Members agreed that this conclusion related to the efficacy of lycopene rather than its safety and therefore was not contradictory to the recommendation they had made to the TGA.

### 7. Safety reviews

#### 7.1 Vitamin B6 (pyridoxine, pyridoxal, pyridoxamine)

Currently in Australia, pyridoxine, pyridoxal and pyridoxamine (vitamin B6) are classified in the SUSDP as Schedule 4 substances (prescription only). However medicines containing vitamin B6 are exempt from scheduling if they contain no more than the equivalent of 50 mg pyridoxine per recommended daily dose, or are labelled with one of two alternate warning statements advising that pyridoxine may be dangerous when used in large amounts for a long time. In New Zealand, in contrast, no restrictions are placed on the use of vitamin B6 under their poisons scheduling.

The NDPSC Trans-Tasman Harmonisation of Scheduling Working Party has sought advice from CMEC on the safety of vitamin B6, specifically the dose-response relationship of peripheral neuropathy and the likely safe level of exposure for long-term supplement use. The aim of the Working Party is to determine if consistency can be achieved between Australia and New Zealand in controls over access imposed through poisons scheduling, and in the associated labelling and packaging requirements.

A TGA officer outlined the current processes for poisons scheduling across Australia.

**Present discussion:**

Copies of three international reviews of the safety of vitamin B6 were provided to members to assist with the discussion of this agenda item. These reviews had been conducted in three jurisdictions (UK, EU and USA) and had reached three different recommendations about safe upper daily intakes of this vitamin (10, 25 and 100 mg respectively). These overseas reviews confirm the need for some form of control over the supply of vitamin B6 as they each conclude that there is a definite risk of the development of peripheral neuropathy in association with long-term use of high doses of vitamin B6. The extent of risk depends on both dose and duration, with neuropathy developing in some cases on doses as low as 50-100 mg/day when taken over extended periods of time.

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Australia’s 50 mg cut-off, before labelling or access restrictions apply to products containing vitamin B6, sits midway between the upper tolerable intake levels determined independently by three expert overseas committees. Current evidence does not indicate that the development of pyridoxine-induced peripheral neuropathy is a significant safety issue in Australia. Over the last 20 years there have been a total of 98 reports to the Australian Adverse Drug Reactions database that have been associated with pyridoxine, but there does not appear to be a consistent pattern to these reactions. There have only been 14 reports where pyridoxine was the sole suspected agent, and only two of these where causality was rated as certain. Neither of these two reactions involved neurological effects.

The current requirements imposed through poisons scheduling appear to have limited the proliferation of high dose vitamin B6 products that are more likely to be associated with development of peripheral neuropathy. It appears that most of the large number of products included in the ARTG that contain vitamin B6, contain less than 50 mg of the vitamin per dose unit.

Based on the balance of evidence, the current Australian restrictions are considered appropriate. On the other hand, there is no evidence to demonstrate that higher doses of vitamin B6 are safe.

Members made the following recommendation to the TGA:

**Recommendation 25.11**

CMEC recommends to the TGA that the current 50 mg daily dose limit (for products containing pyridoxine/pyridoxal/pyridoxamine) for the application of a label warning is scientifically justified. CMEC considers that pyridoxine-induced peripheral neuropathy remains a concern with high doses of pyridoxine, but notes that, under the current Australian regulatory requirements for pyridoxine, no significant safety problems appear to have arisen.

8. **Registration applications**

No matters were considered under this agenda item.

9. **Variation to a registered product**

No matters were considered under this agenda item.

10. **Matters referred from within the TGA**

10.1 **Report from the Adverse Drug Reactions Advisory Committee (249th meeting)**

Members noted a summary of reports from the 249th meeting of ADRAC, held on 15 December 2000.
Present discussion:

Members noted a report of an apparent interaction between St John’s Wort (*Hypericum perforatum*) and an oral contraceptive. This is the first time this predicted interaction has been observed in Australia. Advice issued by the TGA in 2000 about drug interactions associated with use of St John’s Wort included specific advice in relation to oral contraceptives.

10.2 *Aristolochia* surveillance update

Members noted a summary report from the TGA on the *Aristolochia* surveillance analytical program testing results.

The Chairman advised that the United Kingdom is intending to prohibit the importation of products containing *Aristolochia* or herbs commonly mistaken for *Aristolochia*, such as *Stephania*. There was general discussion on mechanisms to control the importation of *Aristolochia* into Australia.

10.3 Transmissable spongiform encephalopathies

Members were advised that the TGA is developing a strategy for establishing and mitigating the risk of exposure to transmissible spongiform encephalopathies (TSEs), particularly bovine spongiform encephalopathy (BSE), for all therapeutic goods. This strategy is vital because many medicines contain ingredients of animal origin. The TGA will be developing a hierarchy of risk for medicinal substances and products. TGA action will be in line with developing international requirements. Members will be kept informed of developments in this area.

10.4 House of Lords report on complementary and alternative medicines

Members noted an extract from the November 2000 report of the UK House of Lords inquiry into complementary and alternative medicine.

One issue raised in the UK report related for the need for publicly accessible, reputable information on complementary medicines. Members discussed briefly the issue of consumer education on complementary medicines.

The Chairman outlined European Union proposals to prevent products that are non-traditional mixtures of complementary medicine substances (such as echinacea combined with zinc) from claiming to be traditional medicines.

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 25th meeting.
**Item 2**  
Minutes of CMEC’s 24th meeting  

Recommendation 25.1  

CMEC confirms that the draft Minutes of its previous meeting (CMEC 24, 1 December 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’)  

Recommendation 25.2  

CMEC recommended the adoption of a number of minor amendments to the Guidelines (November 2000 version). CMEC also looks forward to receiving a draft, simplified version of the Guidelines, being developed by the Complementary Healthcare Council of Australia for industry, to facilitate future consideration of this matter.

**Item 5.1.1 Phenylalanine warning statements**  

Recommendation 25.4  

CMEC noted that no substantial issues had been raised during stakeholder comment on the proposed label warning statement (“Do not use if pregnant or likely to become pregnant”) for products containing more than 500 mg L-phenylalanine per recommended daily dose. Members noted that the Therapeutic Goods Regulations will be amended to require the use of this warning statement on listed medicines.

**Item 6.1 Conjugated linoleic acid 60%**  

Recommendation 25.5  

CMEC recommends to the TGA that conjugated linoleic acid 60% is not suitable for use as an active or excipient ingredient in listable therapeutic goods as there is insufficient evidence to support its long-term safety for human use, particularly that associated with the $trans$-10, $cis$-12 form of linoleic acid.

**Item 6.2 Sugar cane wax alcohols**  

Recommendation 25.6  

CMEC recommends to the TGA that ‘sugar cane wax alcohols’ is suitable for use as an active ingredient in listable therapeutic goods, provided that the recommended daily dose of the substance does not exceed 12 mg, and that goods containing the substance carry the following label advisory statement:

“Not recommended for use by pregnant and lactating women” (or words to that effect).
<table>
<thead>
<tr>
<th>Item 6.3</th>
<th>Thiamine phosphoric acid ester chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 25.7</strong></td>
<td></td>
</tr>
<tr>
<td>CMEC recommends to the TGA that ‘thiamine phosphoric acid ester chloride’ is suitable for use as an active ingredient in listable therapeutic goods, without any substance-specific restrictions on its use.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Item 6.5</th>
<th>(S)-S-adenosyl-L-methionine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 25.9</strong></td>
<td></td>
</tr>
<tr>
<td>CMEC recommends to the TGA that (S)-S-adenosylmethionine is suitable for use as an active ingredient in listable therapeutic goods, provided that the following conditions are met:</td>
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<tr>
<td>• only the p-toluene sulfonate and sulfate salts (or a mixture thereof) are used;</td>
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<td>• these substances are only produced by fermentative processes; and</td>
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<tr>
<td>• picrolonic acid is not used in the manufacturing process.</td>
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<table>
<thead>
<tr>
<th>Item 6.6</th>
<th>Lycopene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 25.10</strong></td>
<td></td>
</tr>
<tr>
<td>CMEC recommends to the TGA that lycopene is suitable for use as an active ingredient in listable therapeutic goods, provided that it is stabilised to minimise degradation.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Item 7.1</th>
<th>Safety review of vitamin B6 (pyridoxine, pyridoxal, pyridoxamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 25.11</strong></td>
<td></td>
</tr>
<tr>
<td>CMEC recommends to the TGA that the current 50 mg daily dose limit (for products containing pyridoxine/pyridoxal/pyridoxamine) for the application of a label warning is scientifically justified. CMEC considers that pyridoxine-induced peripheral neuropathy remains a concern with high doses of pyridoxine, but notes that, under the current Australian regulatory requirements for pyridoxine, no significant safety problems appear to have arisen.</td>
<td></td>
</tr>
</tbody>
</table>

12. **For Information**

No matters were considered under this agenda item.

13. **Action list from previous CMEC meetings**

The Action List for CMEC Meetings was included in the agenda papers but not discussed at this meeting.
14. **Other business**

Five matters were raised under this agenda item.

The meeting closed at 4.00 pm on Friday 2 February 2001. The next meeting is to be held on Friday 23 March 2001.