CMEC 44
Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Forty-fourth Meeting
13 February 2004

Abbreviations:
ADEC Australian Drug Evaluation Committee
ADRAC Adverse Drug Reactions Advisory Committee
ADRU Adverse Drug Reactions Unit (of TGA)
AQIS Australian Quarantine Inspection Service
ARTG Australian Register of Therapeutic Goods
ASMI Australian Self Medication Industry
BP British Pharmacopoeia
BPC British Pharmaceutical Codex
BSE Bovine spongiform encephalopathy
CHC Complementary Healthcare Council of Australia
CMEC Complementary Medicines Evaluation Committee
DSEB Drug Safety and Evaluation Branch
ELF Electronic Lodgement Facility
EP European Pharmacopoeia
FSANZ Food Safety Australia and New Zealand
LOAEL Lowest Observable Adverse Effect Level
MEC Medicines Evaluation Committee
NDPSC National Drugs and Poisons Schedule Committee
NOAEL No Observable Adverse Effect Level
OCM Office of Complementary Medicines
PBS Pharmaceutical Benefits Scheme
SUSDP Standard for the Uniform Scheduling of Drugs and Poisons
TGA Therapeutic Goods Administration
TGAL Therapeutic Goods Administration Laboratory Branch
TSE Transmissible spongiform encephalopathies
The forty-fourth meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in the Kensington Room, Stamford Hotel, Sydney from 9.30 am to 3.30 pm on Friday 13 February 2004.

Members of CMEC present were:

  Professor Tony Smith (Chair)
  Dr Vicki Kotsirilos
  Associate Professor Douglas Moore
  Professor Stephen Myers
  Dr John Ryan
  Mr Kevin Ryan
  Professor Gillian Shenfield
  Dr Iggy Soosay
  Professor Bill Webster
  Associate Professor Heather Yeatman

Present from the Therapeutic Goods Administration (TGA) were:

  Dr David Briggs
  Dr John Hall
  Dr John McEwen
  Mr Karl Skewes

Attending from TGA for the presentation of an agenda item:

  Mr Michael Wiseman
  Mr Shaun Flor

1. Procedural Matters
1.1 Opening of Meeting

The Chair opened the meeting at 9.30 am and welcomed CMEC Members and TGA staff.

1.2 Apologies

There were no apologies recorded for this meeting.

1.3 Conflict of Interest

Members submitted conflict of interest declarations specific to agenda items for this meeting to the Chair.
2. Confirmation of Minutes of CMEC 43 (28 November 2003)

Members accepted the minutes of the forty-third meeting of CMEC as an accurate record of proceedings, subject to minor amendments.

*CMEC Recommendation:*
Members made the following recommendation:

**Recommendation 43.1**

CMEC confirms that the draft Minutes of its previous meeting (CMEC 43, 28 November 2003), 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 (Guidelines)

CMEC did not consider any matters under this agenda item.

4. CMEC Working Party on Herbal Medicine Issues

CMEC did not consider any matters under this agenda item.

5. Action Arising from Previous Meetings

CMEC considered one item.

6. Evaluation of New Substances
   6.1 Active Hexose Correlated Compound

CMEC considered one item and made one recommendation.

7. Safety or Efficacy Reviews
   7.1 Safety review: Hesperidin

*Background*

TGA recently amended the entry for “bioflavonoids” in Schedule 4 of the Therapeutic Goods Regulations (the “Regulations”) and replaced it with the new Australian Approved Name of "citrus bioflavonoids extract." In addition, TGA has undertaken to update the compositional guideline for "citrus bioflavonoids extract". The purpose of the name change in the Regulations
was to provide clarification of the nature of the substance; which the current compositional
guideline described as a “a natural extract derived solely from citrus fruit.” More specifically,
Schedule 4 of the Regulations did not contain entries for two of the major citrus bioflavonoids,
hesperidin and rutin. However, TGA noted that hesperidin and rutin have been included in a
number of listed medicines on the basis that they are bioflavonoids. Therefore, TGA conducted
a safety assessment of these two substances to determine their suitability for continued inclusion
in listed medicines and to develop guidelines for the quality and composition of hesperidin and
rutin. The safety assessment of rutin appears in a separate report under agenda item 7.2.

Characterisation of hesperidin
The bioflavonoid, hesperidin, is a water-soluble compound with antioxidant properties and is
widely distributed in the plant kingdom. Hesperidin is particularly concentrated in citrus rinds as
a non-bitter tasting flavonoid glycoside.

Hesperidin is an Australian Approved Name (AAN) and it is a flavanone, which is a sub-class of
the flavonoids. Flavonoids are a family of natural substances ubiquitous in the plant kingdom, as
they occur in all higher plants. These low molecular weight compounds are found in vascular
plants and are accessible to humans and animals through their diet.

Hesperidin does not have a monograph in the current European Pharmacopoeia (Ph. Eur.),
British Pharmacopoeia (BP) or United States Pharmacopoeia (USP).

History and pattern of use
A variety of flavonoid products are either being actively developed or currently sold worldwide
as dietary supplements and/or herbal remedies. Citrus bioflavonoids and related substances are
reported to be widely used in Europe to treat diseases of the blood vessels and lymph system,
including haemorrhoids, chronic venous insufficiency, easy bruising, nosebleeds, and
lymphoedema following breast cancer surgery. These compounds are thought to work by
strengthening the walls of blood vessels.

Hesperidin and bioflavonoid deficiencies in general, have not been reported. Bioflavonoid
supplements are not required to prevent deficiencies in people eating a healthy diet.

Worldwide, hesperidin is present in nutritional supplements such as vitamin C with
bioflavonoids. A typical dose in these products is about 50 mg. Hesperidin is available in
hesperidin-complex supplements. Doses for this type of supplement are usually 500 mg to 2 g
daily. Healthcare practitioners commonly recommend 1,000 mg of citrus flavonoids taken one
to three times per day.

Products on the Australian Register of Therapeutic Goods (ARTG)
There are 209 products on the ARTG containing hesperidin and over 350 containing citrus
bioflavonoid complex. Most products are listed rather than registered with 16 being export
listed. Hesperidin is from citrus extracts or in bioflavonoid complexes. Fifty products, out of
193, for supply in Australia were investigated for their composition. Products in the form of
powders make up 24% of these products with an average of 50 mg hesperidin /g powder (range
= 5-113 mg/g). Sixteen percent of the products are in the form of capsules with the remainder
(60%) in tablet form. The capsules and tablets have an average of 12 actives, 7 excipients, and 42 mg of hesperidin (range = 0.6-250 mg/tablet or capsule). Sixty-eight percent of the capsules and tablets contain additional bioflavonoids (average amount = 52 mg). Rutin is also present in 76% of these products with an average content of 43 mg. Fifty-two percent of the 50 products are vitamin C preparations. Only two products are indicated as bioflavonoid preparations - several products are multivitamin/mineral supplements with only small amounts of hesperidin.

**Biological activity**
There is little information in the literature about the pharmacokinetics of hesperidin in humans. It is unclear whether absorption of hesperidin from the intestine is as an intact glycoside. The aglycone hesperetin is detected in the serum following ingestion and may possibly be formed prior to, or following absorption. Hesperetin may undergo glucuronidation in the wall of the intestine, as well as in the liver. Hesperetin is detected in the urine within three hours after ingestion of hesperidin.

The gastrointestinal metabolism of flavonoids has been variously reported to be dependent on intestinal microflora. Microflora residing in the intestine can release enzymes to gradually hydrolyse the glycosides into aglycones, which are absorbable by the intestine. Aglycones not absorbed in the small intestine can thereafter be degraded by colonic microflora into phenolic acids. After oral intake, deglycosylation of flavonoid glycosides has been proposed as the first stage of metabolism in the gastrointestinal tract.

Flavonoids may undergo reactions such as hydroxylation, methylation and reductions. Conjugation reactions with sulfate and/or glucuronic acid appears to be the most common pathway for flavonoid metabolism. The conjugated metabolites of flavonoids are still believed to possess antioxidation ability *in vivo*, although they may be weaker than the aglycone parent forms.

The sulfates and glucuronides of flavonoids are ionised under physiological pH and very soluble in water; therefore, they are readily excreted by animals into bile and urine. When excreted into bile, the conjugated metabolites are passed into the duodenum and metabolised by enterobacteria, which hydrolyse the sulfates/glucuronides and further fragment the flavonoid aglycones into aromatic acids. The resulting metabolites may be reabsorbed and enter an enterohepatic circulation to result in a second peak of serum profile. The structure of flavonoid conjugates determines the extent of biliary excretion and enterohepatic circulation. The half-life of elimination also can be prolonged. The variation of urinary excretion of flavonoid metabolites among individuals is very large.

**Pharmacology**
Most pharmacology studies have been *in vitro* and there are several animal studies but only a few human studies done especially with diosmin-hesperidin combination products.

A deficiency of hesperidin in the diet has been reportedly linked with abnormal capillary leakiness as well as pain in the extremities causing aches, weakness and night leg cramps. Additionally, hesperidin and other flavonoids have been claimed to modulate the activity of various enzymes that positively influence normal as well as malignant cells and have noted...
anticancer activity. Supplemental hesperidin may also help reduce oedema or excess swelling in the legs due to fluid retention. Some evidence suggested there is a possible role for citrus flavonoids in the prevention of lifestyle-related diseases because of their beneficial effects on bone and lipids.

**Toxicology**

There is a paucity of human toxicological studies for hesperidin alone.

One animal study determined that acute toxicity of hesperidin in mice was low with an LD₅₀ for intraperitoneal administration equal to 1 g/kg. Researchers in another study, which investigated the anti-inflammatory and analgesic activity of hesperidin in rats, calculated an LD₅₀ of > 2 g/kg for hesperidin suspended in olive oil administered by gavage. In addition, using a gastrolesive test in male rats, the study showed that hesperidin did not cause either hyperaemia or gastric ulcers at a dose of 200 mg/kg by gavage. Other research showed that a product, which contained 90% diosmin and 10% hesperidin, has an oral LD₅₀ of more than 3g/kg in rats and the absence of any toxic effect after repeated oral dosing for 13 and 26 weeks in the rat and primate. In a chronic toxicity study, the lowest published oral toxic dose (TDLo) for tumourigenic effects in the rat was 12600 mg/kg/day.

Extensive investigations of diosmin and hesperidin have found them to be essentially nontoxic and free of drug interactions. This combination was given to 50 pregnant women in a research study. The exposure to hesperidin did not affect pregnancy, foetal development, birth weight, infant growth, and feeding.

In one study methyl hesperidin was given to pregnant rats by oral intubation during days 7 to 17 of gestation at dose levels of 0, 2, 4, and 8 g/kg, and its teratogenic effect was examined in the foetuses. No changes in maternal body weight gain, food consumption and general symptoms were found in the methyl hesperidin-treated groups. There was no evidence of an increase in foetal death or of malformation attributable to the treatment with methyl hesperidin in any of dose levels examined. The authors concluded that methyl hesperidin had no teratogenic effect in rats under the experimental conditions.

In a study using female rats, researchers concluded that hesperidin exhibited anti-inflammatory activity without inducing serious adverse reactions. They also found that hesperidin does not cause gastric mucosal injury.

Methyl hesperidin is a naturally occurring flavonoid contained in citrus fruits and is frequently used as a food additive giving an artificial yellow colour to beverages. Its properties are similar to those of hesperidin. In the subchronic toxicity study of methyl hesperidin in mice, the flavonoid was administered to groups of ten males and ten females in dietary levels of 0, 0.3, 0.6, 1.25, 2.5, and 5.0% for 13 weeks. No significant treatment-related differences were found in data for body weights, food and water consumption, haematology, clinical chemistry, and organ weights. In addition, no effects of treatment were observed on gross and histopathological examination of the major organs.
Researchers conducted a long-term carcinogenicity study with mice that received varying dietary concentrations of methyl hesperidin. Administration of methyl hesperidin continued for 96 wk and then the mice were maintained on a basal diet for an additional 8 wk. Growth retardation during the experiment with final changes in organ weights were observed in females given the 1.25% dose of methyl hesperidin and in both sexes receiving the 5.0% treatment. However, no biologically significant effects were evident with respect to mortality or clinical signs. Treatment with methyl hesperidin did not result in any changes in haematology, clinical chemistry and urinalysis data. On histological examination, no significant alteration of non-neoplastic and neoplastic lesion incidence was observed in treated mice. Therefore, the results indicated that methyl hesperidin lacked any carcinogenicity for mice in the 96-wk feeding regimen used in this study.

Clinical
There were many (> 30) clinical trials for a combination product, which contained flavonoids expressed as hesperidin (50 mg) and diosmin (450 mg). Since the product only contained 10% hesperidin these clinical trials are not summarised in the report. However, several thousand patients have been involved in well-conducted clinical trials, which provide some indication of the safety of hesperidin. The length of the clinical trials varied from about two weeks up to one year with the usual dose being 500 mg twice a day (900 mg diosman, 100 mg hesperidin). Reviews indicate that few adverse reactions have been found in clinical trials. Mild adverse reactions recorded in some trials were gastrointestinal and autonomic in nature. A clinical trial conducted for one year with a dosage of two 500 mg tablets per day revealed that haemodynamic parameters (systolic and diastolic blood pressure) as well as laboratory parameters (haematology, liver, and renal function, metabolic) were uninfluenced by the treatment.

Adverse reactions
Hesperidin and citrus bioflavonoids, in general, appear to be safe with few (if any) adverse reactions in animals or humans reported. A TGA Library literature search failed to find reports of adverse reactions to hesperidin.

The Australian Adverse Drug Reactions (AADR) database holds seven reports for products containing hesperidin. The causality rating assigned to each of the reports for products containing hesperidin was that it was a "possible" causative agent. However, all of the products have multi-ingredient formulations and, therefore it is not possible to determine if hesperidin was the only causative ingredient. Five of the adverse reactions appear to be allergic in nature and may be due to herbs in the formulations.

Contraindications
One source noted that bioflavonoids, including hesperidin, tend to reduce blood platelet stickiness and therefore individuals taking “blood thinners” should consult with their physician prior to commencing supplementation. Hesperidin, along with other bioflavonoids, was found to interact with daunomycin in cultivated endothelial cells.

Present discussion
A Member remarked that it would be difficult to make an adverse finding about a component that was essentially 14 % of citrus peel. Although the safety report did not mention the volume
or comprehensiveness of the data evaluated, there had been a few animal studies undertaken with hesperidin. Notably, one long-term study showed that methyl hesperidin did not demonstrate carcinogenicity when fed to mice. The Member commented that apart from the potential for an anti-platelet effect, there appeared to be no safety concerns for hesperidin.

Members noted that the review highlighted the need for ascorbate complex (which contains bioflavonoids) and not ascorbic acid alone, for the effective treatment of scurvy. One Member mentioned that there were a number of products currently on ARTG that contained this ascorbate complex. The Member added that these complexes also had a number of other significant biological roles eg. antioxidant activity. The Member then commented that it appeared that hesperidin had no significant safety concerns and that not approving it for use in Listed medicines could in fact, be potentially detrimental from a public health and safety perspective.

A TGA officer remarked that one product on ARTG had been available to the Australian public for the last 40 years or so. Originally, the product was touted as a new generation vitamin C over-the-counter medicine, as it also contained citrus bioflavonoids. Australians have been exposed to this product for some time with little to no reported adverse reactions to date, thus confirming the safety profile of the bioflavonoids.

One Member commented that in developing the compositional guidelines for hesperidin, the identification tests should include reference to the substance complying with a certified and authenticated reference standard. A TGA officer confirmed that this was the usual requirement in developing the compositional guidelines for a new substance if it could not be alternatively characterised.

Members agreed that hesperidin appeared to have no significant safety concerns and was therefore, suitable for use as an ingredient in listed medicines.

_CMEC Recommendation:_
Members made the following recommendation:

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<tr>
<th>Recommendation 44.3</th>
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<td>CMEC noted the review of safety of hesperidin conducted by the TGA and recommends that it is suitable for use as an ingredient in listed medicines.</td>
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### 7.2 Substance safety review

The Committee considered one item and deferred a final decision on the substance to a subsequent meeting of CMEC.
8. Registration Applications

CMEC considered one item and made one recommendation.

9. Variation to a Registered Product

CMEC did not consider any matters under this agenda item.

10. Matters referred from within the TGA

10.1 – 10.2 CMEC considered two items and made a recommendation on one item.

10.3 Ginseng and pregnancy

Background
At the last meeting of CMEC (November 2003), Members noted a Science Daily News report of a study by Chan et al. 2003 (cited in the journal, *Human Reproduction*), which investigated potential teratogenic properties of one of the principal active ingredients of Ginseng, ginsenoside Rb-1. The authors of the article had concluded, "use of ginseng during first trimester of pregnancy should be with caution". As a result of the publication, the international media (following an initial BBC news report) issued a warning to the public without any scrutiny of the findings by appropriate health authorities in terms of relevance of the study to human health. The results of this *in vitro* study suggested that ginseng was teratogenic.

Although widely reported in popular media, CMEC Members were subsequently informed that there were methodological concerns with the study and that the results should be interpreted with caution. TGA prepared a critical appraisal of the study for Members to show the need for appropriate interpretation of experimental results, which may bear upon the use of medicines containing ginseng in pregnancy.

TGA asked CMEC to provide advice as to whether, on the basis of these research findings, there is any basis for modifying the way ginseng is currently regulated.

Present discussion
A Member noted that the authors of the publication had used rat embryo *in vitro* and that any substance at particular concentrations would adversely affect the embryos. There were no details on whether the amount of ginsenosides used *in vitro* was comparable to that normally achieved in the blood of humans who consumed ginseng. The Member commented that therapeutic goods that contained ginseng would be unlikely to produce blood levels of ginsenosides that caused the embryonic teratology detected *in vitro* by the researchers. Another Member commented that humans also tended to consume ginseng intermittently and not on a continual basis.

Members agreed that based on the current scientific evidence, no changes were needed to the way in which ginseng is regulated as an ingredient in listed medicines.
CMEC Recommendation:
Members made the following recommendation:

**Recommendation 44.7**

CMEC recommends to TGA that, based on current scientific evidence, ginseng does not require any changes to the way in which it is regulated as an ingredient in listed medicines.

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 44th meeting:

**Item 2 Minutes of CMEC’s 43rd. Meeting**

**Recommendation 44.1**

CMEC confirms that the draft Minutes of its previous meeting (CMEC 43, 28 November 2003), as amended, are a true and accurate record of that previous meeting.

**Item 6.1 Evaluation of New Substance: Active Hexose Correlated Compound**

**Recommendation 44.2**

CMEC recommends to TGA that, on the basis of the data evaluated, active hexose correlated compound is not suitable for use as an ingredient in listed medicines.

**Item 7.1 Safety Review: Hesperidin**

**Recommendation 44.3**

CMEC noted the review of safety of hesperidin conducted by the TGA and recommends that it is suitable for use as an ingredient in listed medicines.

**Item 10.3 Ginseng and pregnancy**

**Recommendation 44.7**
CMEC recommends to TGA that, based on current scientific evidence, ginseng does not require any changes to the way in which it is regulated as an ingredient in listed medicines.

12. **For Information**

12.1 **Kava (Piper methysticum) – an update**

A TGA officer asked Members to note an amendment to the Therapeutic Goods Regulations (1990) that restricts the therapeutic use of *Piper methysticum* (kava) in accordance with the recommendations made by CMEC at meeting number 41.

12.2 **Demonstration of Electronic Lodgement Facility (ELF 3) for Listed medicines**

Two TGA officers provided CMEC with a practical demonstration on how the Electronic Lodgement Facility (ELF 3) works for lodging an application with TGA for a listed medicine.

13. **Other business**

There was no other business for consideration by CMEC.

The Chair closed the meeting at 3.30 pm.