Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 66 COMPLEMENTARY MEDICINES EVALUATION COMMITTEE

Extracted Ratified Minutes
Sixty-sixth Meeting
18 April 2008

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit
ANZTPA	Australian and New Zealand Therapeutic Products Agency
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
BMI	Body Mass Index
BP	British Pharmacopeia
CMEC	Complementary Medicines Evaluation Committee
CRC	Child-resistant closure
ECCMHS	Expert Committee on Complementary Medicines in the Health System
GMP	Good Manufacturing Practice
JAMA	Journal of the American Medical Association
LD_{50}	Lethal Dose 50%
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drug and Poison Scheduling Committee
NPS	National Prescribing Service
OCM	Office of Complementary Medicines
OICG	OCM Industry Consultation Group

OTC	Over-The-Counter
PRC	People's Republic of China
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
VEBCEAG	Vitamin E and Beta-carotene Expert Advisory Group

The Complementary Medicines Evaluation Committee (CMEC) held its sixty-fifth meeting in Conference Room 1, Therapeutic Goods Administration, 136 Narrabundah Lane, Symonston, from 8.40 a.m. to 4.35 p.m. on Friday 22nd February 2008.

Members of CMEC present were:
Professor Tony Smith (Chair)
Professor Alan Bensoussan
Dr Lesley Braun
Dr Gary Deed
Dr Vicki Kotsirilos
Ms Karen Martin
Professor Stephen Myers
Dr Richard Oppenheim
Mr Kevin Ryan
Professor Bill Webster
Mr Hans Wohlmuth
Associate Professor Heather Yeatman

Expert Advisors to CMEC present were:
Dr Tim Carr
Mr Philip Daffy
Mr John Lumby (morning session)
Ms Robyn Minski

Present from the Therapeutic Goods Administration (TGA) were:
Professor David Briggs
Dr Andrea Hinschen
Ms Michelle McLaughlin
Ms Nicola Powell
Mrs Diane Wilkinson
Mr Michael Wiseman (afternoon session)

1 PROCEDURAL MATTERS

1.1 Opening of Meeting

The Chair opened the formal part of the meeting at 9:30 am, welcoming CMEC Members, Expert Advisors and TGA staff.

1.2 Apologies

Dr Ruth Lopert (Acting Principal Medical Advisor)

Professor Marc Cohen (Expert Advisor)

Mr Robert Medhurst (Expert Advisor)

1.3 Conflict of Interest

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

1.4 Meeting venues for 2008

Members noted and discussed the confirmed CMEC meeting arrangements for 2008.

2 CONFIRMATION OF MINUTES OF CMEC 65 (22 FEBRUARY 2008)

Members accepted the Minutes of the sixty-fifth meeting of CMEC as an accurate record of proceedings, subject to minor amendment.

Members made the following recommendation:

Recommendation 66.1 CMEC confirms that the draft Minutes of its previous meeting (CMEC 65, 22 February 2008), as amended, are a true and accurate record of that 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 ACTION ARISING FROM PREVIOUS MEETINGS

4.1

CMEC considered one matter under this agenda item.

4.2 Review of *Ligusticum lucidum*

Background

A TGA Officer introduced this item, reminding Members that at CMEC 63, Members considered a safety review of the herbal species *Ligustrum lucidum.* This review was

undertaken because of a potential safety concern with respect to the use of the fresh fruit, and parts other than the seed, of the herb *Ligusticum lucidum.*

However, whilst the safety review was being undertaken, it was discovered that this herb did not have a history of traditional use. In contrast, a herb with a similar name, *Ligustrum lucidum*, was identified as having a long history of medicinal use in TCM. Due to their similar names and the fact that *Ligusticum lucidum* did not appear to be used medicinally, the OCM proposed that the safety concern identified for the herb *Ligusticum lucidum* should, in fact, have been applied to the herb *Ligustrum lucidum.* A safety review of *Ligustrum lucidum* was thus undertaken, following which CMEC recommended that the herb remain suitable for Listing.

Members noted that that the OCM has contacted the sponsors of the 14 medicines included in the ARTG (identified as containing preparations of the ingredient *Ligusticum lucidum*) and requested information regarding these medicines. Collated sponsor responses indicate that none of the medicines are derived from *Ligusticum lucidum*, but rather contain herbal preparations of *Ligustrum lucidum*. All of the affected sponsors have undertaken, or are in the process of undertaking, corrections to the ARTG entry for their medicines, as well as corrections to the medicine labels.

CMEC was therefore asked to consider whether *Ligusticum lucidum* should remain suitable for inclusion in Listed Medicines, given that:

- there is no evidence of traditional medicinal use of the herb; and
- there are no medicines included in the ARTG that contain preparations of this herb.

Discussion

Members unanimously agreed that the herb *Ligusticum lucidum* was not considered suitable for use as an ingredient in Listed medicines, as there is no history of medicinal use for the herb.

Members made the following recommendation:

Recommendation 66.2

CMEC recommends to the TGA that *Ligusticum lucidum* is not suitable for use as an ingredient in Listed medicines.

4.3 Vitamin B6 safety – revised label warning statement

Background

A TGA Officer introduced this item, reminding Members that at CMEC 65 (February 2008), Members discussed the Adverse Drug Reaction Advisory Committee's (ADRAC) concerns that the current label advisory statements for products containing vitamin B6 (within the dose range of 50 to 200 mg) are inadequate to effectively warn consumers of its potential toxicity.

Members noted that at CMEC 65, it was agreed that the potential for vitamin B6 neurotoxicity was a serious concern, and Members endorsed two remedial regulatory measures; to inform medical practitioners *via* the ADRAC bulletin about the need to monitor their patients for the use of vitamin B6 products, and to increase consumer awareness of potential vitamin B

toxicity through describing the early signs of neurological effects on the label of products containing vitamin B6 within the dose range of 50 to 200 mg.

Members were asked to comment on suitable wording for the label advisory statements. Members were also asked to specifically consider what clinical signs should be communicated on the label and whether a reference to vitamin B6 content was necessary.

Discussion

Members supported use of the terms "*tingling, burning or numbness*", rather than "*tingling and/or burning electric shock sensation*" as more meaningful to the consumer.

Members agreed that the warning should convey a sense of urgency and considered that the words "*WARNING – Stop taking this medication"* should be placed at the front of the label advisory statement, noting that the early onset effects of vitamin B6 are reversible, and advice to immediately stop the medication was of prime importance. Members also considered that the words "*as soon as possible*" should be used to prompt consumers to contact their healthcare practitioner.

Members agreed that referring the consumer to a "*healthcare practitioner*" for early onset symptoms was appropriate (as was the specific reference to "*vitamin B6*" in multi-ingredient preparations, in order to help consumers identify the source of the neurotoxic effects).

Members noted the potential for consumer confusion given that the symptoms of carpal tunnel syndrome, for which this medication is commonly used, are similar to the symptoms referred to in the label warning statement. However whilst this issue raised concern, it was pointed out that consumers using this medication for the relief of carpal tunnel syndrome would likely be undergoing management and/or treatment for this condition under the direction of a general practitioner, who would be able to discuss this with their patient.

Overall, Members endorsed two label advisory statements, for both single and multi-ingredients products.

Members made the following recommendation:

Recommendation 66.3

CMEC recommends to the TGA that the current label warning statement for products containing from 50 to 200 mg vitamin B6 (pyridoxine, pyridoxal, pyridoxamine) per recommended daily dose be amended as follows:

for single ingredient products:

"WARNING – Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible."

for multi-ingredient products:

"WARNING – Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. Contains vitamin B6."

4.4

CMEC considered one matter under this agenda item.

4.5

CMEC considered one matter under this agenda item.

4.6

CMEC considered one matter under this agenda item.

5 EVALUATION OF NEW SUBSTANCES

CMEC did not consider any matters under this agenda item.

6-7 SAFETY OR EFFICACY REVIEWS

7.1 Review of *Caesalpinia sappan*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern had been identified with respect to the use of the heartwood of the herb *Caesalpinia sappan* in pregnancy.

The Committee noted that *C. sappan* is currently a permitted ingredient in Listed medicines, with no restrictions placed on its use. There are currently three medicines Listed in the ARTG that include preparations the heartwood of *C. sappan* as an ingredient; one of these medicines is for oral administration, whilst the other two are for topical administration. The preparations of the ingredient include an infused oil, an aqueous extract and an ethanolic extract.

The Officer informed Members that the plant has a long history of use in Traditional Chinese Medicine (TCM) as an emmenagogue, an astringent, an antibacterial, an analgesic and to invigorate the blood. Traditional texts and research papers refer to the heartwood (the older, non-living central wood) as the plant part used. No information was found regarding the use of the infused oil applied topically. However, a decoction of *C. sappan* has been used traditionally as a topical application.

The Committee was informed that three traditional references contraindicated the use of *C. sappan* during pregnancy. In addition, *C. sappan* was included in four animal studies examining the antifertility and the uterine stimulating effects of certain herbs. One study referred to the use of *C. sappan* as an abortifacient in Thailand, and another study referred to its use in India as a uterine stimulant. All four studies reported no effects on fertility, nor found any uterine stimulating effects from *C. sappan*. However, all studies were of questionable quality.

The Officer also commented on another study where *C. sappan* was found to inhibit motility and induce coagulation in human sperm *in vitro*. However, the methodology was not included for this study.

The Officer stated that reproductive toxicity studies in humans are lacking and that no reports of adverse effects for *C. sappan* have been located to date. The review concluded that there appears to be no toxicity associated with use of *C. sappan*. However, one study showed that an extract of *C. sappan* inhibited the growth of normal human embryonic cells *in vitro*.

The Committee was asked to consider if the long history of use of *C. sappan* with no reported side effects, and the apparent low toxicity of the herb, provide an assurance of safe use in Listed Medicines. Further, CMEC was asked to consider whether the current unlimited use of *C. sappan* in Listed medicines presents an unacceptable safety risk for use during pregnancy.

Discussion

Traditional use and traditional contraindication

A Member stated that in the TCM paradigm, *C. sappan* is considered to be a "blood moving" (used to remove blood clots and alleviate bruising) herb and that all herbs with 'blood moving' properties routinely warn against use in pregnancy. The Member questioned how the Committee could deal with traditional pregnancy contraindications in relation to this TCM category of herbs, particularly where the traditional contraindication was not supported by studies using the herb. The Member added that there was also a conundrum where a herb has a traditional contraindication in pregnancy, but is also used traditionally in pregnancy e.g. don quai.

Members also noted the difficulty experienced when comparing traditional and scientific information, as both use different terminology.

Scientific studies

With regards to the presented data, a Member noted that there were no single or repeat dose toxicity studies, and that the limited studies that were available, were poorly documented. Members noted the fertility study on mice by De S.Matsui *et al*. (1971), in which *C. sappan* was found to have no effect on fertility, no overt toxicity and did not interrupt the oestrus cycle. A study by Prakash (1984) in which the embryo-toxic effect of *C. sappan* (on pregnant mice, rats and golden hamsters) was investigated, reported no toxic effects. Moreover, a study by Kapur (1948) stated that *C. sappan* did not exert any uterine or abortifacient effects.

Members also noted the Shih *et al*. (1990) study on human sperm motility and commented that the *in vitro* study required a large concentration of an aqueous extract of *C. sappan* (2.5 mg/mL) to reduce sperm motility to 50% of the control medium. Members therefore considered that the results of this study were not physiologically relevant, adding that the author's conclusion that the herb may have potential for a male contraceptive effect was extremely optimistic.

Members noted that on the basis of the available data, there appeared to be no apparent safety concern for *C. sappan*.

Restrictions

Members discussed the idea of a restriction on plant part and/or preparation. They agreed that this would not inform a consumer of the traditional use of the herb as an abortifacient, and questioned what would happen if an adverse event occurred in the future. Members also discussed the use of warning statements as a means to advise consumers of traditional concerns, and agreed on the need for the education of the public and health care professionals, stating that appropriate information on the TGA's website would be beneficial.

A TGA Officer informed the Committee that the National Prescribing Service (NPS) was currently seeking advice from an expert group on ways to improve public knowledge, in particular, in relation to the safety of complementary medicine use in pregnancy.

A Member agreed that informing consumers was important, but expressed concern that a warning statement could open the medicine up for abuse i.e. the herb could be taken in an attempt to induce abortion.

A Member commented that whilst in previous considerations, the Committee had recommended removing a herb's eligibility for Listing based on good quality *in vivo* studies, in this case there was not strong evidence of a safety concern in pregnancy and not enough information to impose any regulatory restriction, in particular, that of a warning statement. The Member added that the quantities of the ingredient included in current medicines in the ARTG were well below the recommended daily dosage of the herb, which provided some safety assurance.

Other Members considered that imposing a restriction on dose and preparation type based on pharmacopeial standards, for example the People's Republic of China (PRC) pharmacopoeial monograph, may limit potential safety concerns by confining preparations to traditional forms only. Members discussed the potential contradiction of accepting some traditional recommendations of the PRC monograph (such as preparation and dosage) but not accepting the traditional pregnancy contraindication included in this same text, but considered that as these references were not currently at hand, any perceived inconsistencies could not be adequately identified.

Overall, Members considered that the herb should remain Listable, but the OCM should examine the Chinese, Korean and Indian pharmacopoeias for any applicable dosage and preparation restrictions.

Members made the following recommendation:

Recommendation 66.4

CMEC recommends to the TGA that the use of *Caesalpinia sappan* as an ingredient in Listed medicines should be limited to traditional preparations of the heartwood.

7.2 Review of *Cedrus atlantica*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern had been identified with respect to the use of all plant parts of *Cedrus atlantica* in pregnancy.

Members were advised that *C. atlantica* is a permitted ingredient in Listed medicines with no regulatory restrictions on any plant part or preparation. There are currently 12 Listed medicines in the ARTG containing *C. atlantica* as an ingredient. All of these products contain the essential oil derived from the wood, and all have either topical or inhalation routes of administration.

Members were informed that, traditionally, *C. atlantica* wood essential oil has been used topically for skin complaints, or inhaled for respiratory problems and nervous tension. The safety review revealed one traditional text which cautioned against the use of *C. atlantica* during pregnancy, with no other details provided. The Officer added that other texts did not include this caution.

Members noted that the very limited available literature which addressed the toxicological profile of *C. atlantica*, did not raise any safety concerns regarding the topical or inhalant use of the essential oil of *C. atlantica* wood. Members were informed that it is possible that the confusion in relation to safety during pregnancy, may stem from the fact that the essential oil of *C. atlantica* has the same common name as other herbal species which do have safety

concerns during pregnancy, particularly the thujone-containing essential oil of *Thuja occidentalis.*

CMEC was asked to consider if it was appropriate to place a regulatory restriction on the use of *C. atlantica* in Listed Medicines, based on an unsubstantiated contraindication relating to the use of the herb in pregnancy, in a limited number of traditional texts.

Independent to the issue of safety during pregnancy, CMEC was also asked to note that the current Australian regulations do not impose any restriction on the use of C. *atlantica*. Therefore, the use of different preparation types, different plant parts, and other routes of administration (i.e. internal administration) which are not linked to traditional safe use are permitted. Given the apparent lack of safety data at this time, and the minimal impact on currently Listed products, the Committee was asked to consider if it might be prudent to restrict the use of *C. atlantica* to those uses that are supported by herbal texts and a history of traditional use (i.e. essential oil of wood; topical and inhalant applications). The Committee was advised that such regulatory action would have no impact on Listed medicines currently included in the ARTG.

Discussion

Members commented on the toxicological data on the herb and noted the study by Opdyke (1976) in which both the oral and dermal LD_{50} values of *C. atlantica* in rabbits were reported to be greater than 5g/kg, indicating a very low acute toxicity.

Members also noted that there was no apparent toxicity or adverse events reported in the clinical trial by Hay *et al.* (1998), which investigated an essential oil preparation including *C. atlantica* in the topical treatment of 86 sufferers of *alopecia areata*.

Members agreed that there was no evidence that the herb was taken orally, rather, that the traditional routes of administration were topical or *via* inhalation. Members further agreed that there was no apparent evidence of a safety concern in pregnancy, where the herb *C. atlantica* is administered topically or *via* inhalation.

Members commented that the original safety concern identified for this herb (in relation to pregnancy), was likely to be the result of confusion caused by *C. atlantica* having the same common name (cedarwood) as other unrelated botanical species.

An Expert Advisor informed the Committee that *C. atlantica* essential oil is not commonly self-prescribed by the public, but is commonly used by practitioners. The Advisor was unaware of any reported adverse effects to the herb.

Overall, Members considered allowing *C. atlantica* to remain Listable was appropriate, where restricted to essential oil preparations and dermal or inhalation routes of administration, as supported by traditional use.

Members made the following recommendation:

Recommendation 66.5

CMEC recommends to the TGA that only an essential oil preparation of the wood of *Cedrus atlantica,* when administered topically or via inhalation, is suitable for use in Listed medicines.

7.3 Review of *Selaginella tamariscina*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern had been identified with respect to the use of the whole plant of *Selaginella tamariscina* in pregnancy and its preparation method.

Members noted that *Selaginella tamariscina* is a permitted ingredient in Listed medicines, with no restrictions on any plant part or preparation, and that there were currently two Listed medicines included in the ARTG that contain concentrated water extracts of the ingredient.

The Officer stated that the whole plant is used traditionally. Members noted that there were two methods of preparation for *S. tamariscina* described in the 2005 People's Republic of China (PRC) pharmacopoeial monograph, with different actions and indications provided for each. In the first preparation described, the herb was washed, cut, and sun-dried. A decoction of this preparation was recommended to promote circulation and stimulate menstruation. Uses include amenorrhoea, dysmenorrhoea and abdominal masses. The second preparation was called '*Herba selaginella* (carbonised)' and described the cleaned herb being stir-baked until charred-black. A decoction of this preparation was recommended to remove stasis and stop bleeding. Uses include abnormal uterine bleeding, bleeding from the rectum and rectum prolapse.

Members noted that the PRC monograph cautions against the use of the herb in pregnancy, but provides no further information. This caution was not found in any other literature.

The Officer informed Members that since the CMEC paper was written, the OCM has received the results of a search of the TCM database and Chinese reference texts from the University of Western Sydney. Members expressed their appreciation for this contribution. The TCM database search retrieved 8 references, but a detailed review of these abstracts did not identify any adverse events or toxicity for the herb. The Chinese references revealed one additional text that contraindicated the herb's use in pregnancy in addition to the Chinese pharmacopeia, but again no further details were provided.

The Officer pointed out that, in general, there was a paucity of data relating to the safety or toxicity of the herb. There were no reports of adverse events for the herb, and no scientific data indicating safety concerns either in pregnancy, or otherwise.

Members were asked to consider whether it is appropriate to restrict the use of *S. tamariscina* in Listed medicines, based on an unsubstantiated caution provided in only two traditional texts. In addition, CMEC was also asked to consider if, given the lack of clinical trials and safety data, the use of *S. tamariscina* in Listed medicines should be restricted to traditional preparations. Traditionally, raw *S. tamariscina* is prepared by drying or frying, and traditional extracts are limited to decoctions. Given that there are only two products containing *S. tamariscina* currently included in the ARTG, and that both of these are formulated with aqueous extracts of the herb, the Officer noted that no regulatory impact would be expected from such an action.

Discussion

Members noted that a study by Yang et al (2007), investigating the anti-metastatic activities of *S. tamariscina* on mice lung cancer cells, was of poor quality, and that *S. tamariscina* was employed in very high doses in this study.

Traditional use and contraindication

Members discussed the use of *S. tamariscina* as a "blood moving" herb in TCM, noting that all herbs in this category have a general contraindication in pregnancy, and that the PRC monograph does include a pregnancy contraindication for *S. tamariscina*. However, Members noted that a search of Chinese scientific literature did not reveal any adverse events associated with the herb's use in pregnancy. Members requested that the OCM attempt to contact the PRC to determine, if possible, the basis for the pregnancy contraindication.

In general, Members considered that a history of traditional use provides some assurance of safety and considered that *S. tamariscina* (as traditionally prepared) should remain eligible for Listing. In principle, Members agreed with the restricting *S. tamariscina* to aqueous preparations only, as per the PRC monograph. However, Members expressed concern that too much emphasis was being placed on one traditional pharmacopeia, when there were other pharmacopoeias that also should be considered e.g. Korean, Chinese and Indian pharmacopoeias. Members requested that the OCM consult all relevant pharmacopoeias to clarify what preparations have been used traditionally.

ARTG products

Members discussed issues related to medicinal/traditional interchangeability, given the PRC monograph mentions more than one species. It was noted that medicines on the ARTG should only include those species that are Listable, and that the herbal species used are required to be identified as part of GMP.

Overall, Members agreed that *S. tamariscina* remained suitable for inclusion in Listed medicines, but that the preparations of the herb should be restricted to those preparations reference in traditional pharmacopoeias.

Members made the following recommendation:

Recommendation 66.6

CMEC recommends to the TGA that the use of *Selaginella tamariscina* as an ingredient in Listed medicines should be limited to traditional preparations of the herb.

7.4 Review of *Psoralea corylifolia*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern had been identified with respect to the use of the seeds of *Psoralea corylifolia*, with a maximum daily dose limit of 9 g recommended.

Members noted that currently there are no restrictions on the use of *P. corylifolia* as an ingredient in Listed medicines, and that there are thirty-two oral medicines containing preparations of the herb listed in the ARTG. These medicines contain *P. corylifolia* extracts at doses generally equivalent to less than 1 g/day dried fruit or seed, in combination with numerous other Chinese herbs.

The Officer stated that a diverse range of biological effects have been reported for extracts and constituents of *P. corylifolia*, including a report that a crude 70% ethanol extract of *P. corylifolia* fruit possessed estrogenic activity *in vitro*. Traditionally, *P. corylifolia* has been used in Chinese medicine for complaints relating to the kidneys, and urinary system. The

herb has also been used to treat reproductive symptoms, and as a general tonic to the genital system. Two references list 'abortifacient' as an action for the herb, and one of these also states it is used to prevent early fertilisation.

Members were advised that most Chinese traditional literature refers to the dried, ripe fruit as the part used. However, as a legume, the "fruit" (or pod) contains only one "seed" (legume), and is indehiscent (not opening at maturity), therefore any preparation of the fruit is likely to contain the seed. The constituents of the fruit and seed are reported as virtually identical, with the main constituents being the psoralens.

Members noted that psoralens are known to cause phototoxicity and can sensitise the skin to ultra-violet light, an effect only likely to be achieved at very high doses relative to the recommended therapeutic dose. As the herb is used for the treatment of skin conditions such as leukoderma and psoriasis in Chinese and Ayurvedic traditional medicine, the Officer identified this was a possible concern.

Members also noted that repeat-dose studies conducted in mice and rats, and a reproductive study in mice, reported changes in reproductive organs in both sexes, and female fertility was affected. However, the few toxicology studies conducted with *P. corylifolia* seed/fruit used high doses relative to the amount likely to be consumed in therapeutic products.

No adverse reactions have been reported to the Adverse Drug Reactions Unit (ADRU) of the TGA. However, there were three cases reported in the literature of adverse skin reactions, and one report of a woman experiencing nausea, vomiting and general weakness following an extended period of overdosing on this herb.

Members were asked to consider whether a restriction on the permitted dosage for *P. corylifolia*, and/or the psoralen content, would be appropriate. Further, Members were asked whether it was appropriate to not permit preparations of *P. corylifolia* in Listed Medicines, based on vague and unsubstantiated references to use of the herb as an abortifacient, in some traditional texts.

Discussion

Oestrogenic effect

Members noted that in high enough doses, *P. corylifolia* can have an oestrogenic effect, and may also affect other hormones. However, the dose required for this action was considered to be very high.

Psoralens and Photosensitivity

Members noted the presence of psoralens in *P. corylifolia* and that high doses of *P. corylifolia* resulted in an increase in photosensitivity.

Members discussed the likelihood that an individual might suffer a photosensitivity reaction to the herb. In considering this, Members compared the herb to other substances that also had the potential to increase photosensitivity e.g. celery and St John's wort, noting that in reality, a photosensitivity reaction to these substances was a rare occurrence. Members then discussed whether there would be a cumulative effect with *P. corylifolia* and other medicines that contain psoralen, but considered the evidence for this was only anecdotal.

Whilst some Members considered that there was a likely dose relationship between the herb and photosensitivity, not all Members believed this was clearly established. However, Members generally agreed that there was the potential for photosensitivity to occur with consumption of the herb and that a dosage restriction might therefore be appropriate.

Dose restriction

Members considered that the herb appeared to be toxic in high doses and that a dosage restriction was therefore warranted, whether on the herb itself, or on the psoralen component. As different extraction processes can yield different concentrations of psoralen, it was agreed that placing a restriction on the component itself was most appropriate.

Members discussed an appropriate restriction for psoralen, noting that the there were other sources of, for example, furocoumarins (photosensitizing compounds in the diet and from other medicines), the effect of which, combined with *P. corylifolia*, could potentially be cumulative. Members noted that the upper dietary intake of furocoumarins was 0.02 mg/kg, based on UK dietary figures. However, it was contended that people living in areas of higher environmental exposure to UV light, including Australia, might be more at risk.

Warning Statement

Members also discussed the fact that several medicines are known to increase photosensitivity, individual sensitivity to psoralens is highly varied, and there is therefore potential for increased phototoxicity risk in these consumers. In light of this varied individual susceptibility to psoralens and ability to self-prescribe medicines containing psoralen-containing compounds, Members considered that in the interest of public safety, a statement on the label of medicines containing *P. corylifolia*, warning of the possibility of increased risk of photosensitivity, was warranted.

Plant part restriction

A TGA Officer pointed out that traditional use of the herb involves use of the fruit and seed and questioned whether the use of the herb in Listed Medicines should be restricted to these plant parts. Members considered this appropriate, noting that such a restriction would not have an impact on those medicines currently included in the ARTG.

Product supply information

Members discussed the 32 medicines currently Listed in the ARTG containing the ingredient, noting that information as to whether these were all currently in supply and, if so, in what quantities, was not available in the ARTG records and would only be available directly from the sponsors.

Education

One Member commented that practitioners and consumers should be advised of the cumulative effect that psoralens (obtained in the diet and medications) may have. It was also pointed out that practitioners who extemporaneously prepare medicines are not necessarily aware of this fact and may therefore not warn their patients of the potential for photosensitivity. Members agreed that information regarding photosensitivity reactions from herbs should be accessible to the public. Members also considered that this was a broader issue and could apply to the cumulative effects of medicines in general.

Overall, Members agreed that preparations of the fruit and seed of *P. corylifolia* should remain Listable, with a maximum daily dosage limit on psoralen content of less than 1.1%, and the inclusion of an advisory statement informing of the photosensitising potential of psoralen.

Members made the following recommendation:

CMEC recommends to the TGA:

Recommendation 66.7.1

That the use of *Psoralea corylifolia* as an ingredient in Listed medicines should be limited to preparations of the fruit/seed containing less than 1.1 per cent psoralen per recommended daily dose.

Recommendation 66.7.2

That an advisory statement, informing consumers of the photosensitizing potential of psoralen, be included on any product containing preparations of *Psoralea corylifolia*.

8 REGISTRATION APPLICATIONS

CMEC did not consider any matters under this agenda item.

9 VARIATION TO A REGISTERED PRODUCT

CMEC did not consider any matters under this agenda item.

10 MATTERS REFERRED FROM WITHIN TGA

10.1 Adverse Drug Reactions Advisory Committee (ADRAC) Meeting 306

Complementary medicine issues

CMEC discussed adverse drug reaction reports involving complementary medicines and related issues of interest from ADRAC Meeting 306. Of particular note was the finalisation of the ADRAC review of the Blue Card reporting form for adverse reactions, which Members noted CMEC had previously provided comment on.

Members also noted ADRAC's discussions of the Harvey *et al* paper (*MJA* 2008; 188: 21-25).

Case reports

Members discussed, in detail, case reports of interest from ADRAC Meeting 306.

10.2

CMEC considered one matter under this agenda item.

10.3

CMEC considered one matter under this agenda item.

10.4

CMEC considered one matter under this agenda item.

11 FOR INFORMATION

11.1 Publication - Slatore *et al* 2008: Long term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer

CMEC noted the recent paper published in the journal '*American Journal of Respiratory and Critical Care Medicine*' and the reported increased risk of lung cancer associated with vitamin E supplementation.

A Member remarked that this risk was predominantly confined to smokers taking supplemental vitamin E. They also pointed out two other vitamin E papers, published in 2008, which reported cardioprotective effects of vitamin E supplementation (Ye and Song (February 2008) *European Journal of Cardiovascular Prevention & Rehabilitation* 15(1): 26-34), and no effects of vitamin E supplementation on cancer (Bardia *et al* (2008) *Mayo Clinic Proceedings* 2008; 83(1): 23-34).

11.2 Publication – Cooper *et al* 2007: Public health risks from heavy metals and metalloids present in Traditional Chinese Medicines

CMEC noted the paper published in the '*Journal of Toxicology and Environmental Health*', describing heavy metal and metalloid contamination in TCMs.

12 SPONSOR REPRESENTATIONS TO CMEC

CMEC did not consider any matters under this agenda item.

13 OTHER BUSINESS

CMEC considered one matter under this agenda item.

14 Recommendation Record

Item 2 Confirmation of Draft Minutes of CMEC 65 (22 February 2008)

Recommendation 66.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 65, 22 February 2008), as amended, are a true and accurate record of that meeting.

Item 4.2 Review of *Ligusticum lucidum*

Recommendation 66.2

CMEC recommends to the TGA that *Ligusticum lucidum* is not suitable for use as an ingredient in Listed medicines.

Item 4.3 Vitamin B6 safety - revised label warning statement

Recommendation 66.3

CMEC recommends to the TGA that the current label warning statement for products containing from 50 to 200 mg vitamin B6 (pyridoxine, pyridoxal, pyridoxamine) per recommended daily dose be amended as follows:

for single ingredient products:

> " WARNING – Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible."

for multi-ingredient products:

> " WARNING – Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. Contains vitamin B6."

Item 7.1 Review of *Caesalpinia sappan*

Recommendation 66.4

CMEC recommends to the TGA that the use of *Caesalpinia sappan* as an ingredient in Listed medicines should be limited to traditional preparations of the heartwood.

Item 7.2 Review of *Cedrus atlantica*

Recommendation 66.5

CMEC recommends to the TGA that only an essential oil preparation of the wood of *Cedrus atlantica*, when administered topically or via inhalation, is suitable for use in Listed medicines.

Item 7.3 Review of *Selaginella tamariscina*

Recommendation 66.6

CMEC recommends to the TGA that the use of *Selaginella tamariscina* as an ingredient in Listed medicines should be limited to traditional preparations of the herb.

Item 7.4 Review of *Psoralea corylifolia*

CMEC recommends to the TGA that:

Recommendation 66.7.1

That the use of *Psoralea corylifolia* as an ingredient in Listed medicines should be limited to preparations of the fruit/seed containing less than 1.1 per cent psoralen per recommended daily dose.

Recommendation 66.7.2

That an advisory statement, informing consumers of the photosensitizing potential of psoralen, be included on any product containing preparations of *Psoralea corylifolia*.

The Chair closed the meeting at 4:35 pm.