Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 64 COMPLEMENTARY MEDICINES EVALUATION COMMITTEE

Extracted Ratified Minutes
Sixty-fourth Meeting
14 December 2007

Abbreviations:

ADR	Adverse Drug Reaction
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit
AHMAC	The Australian Health Ministers' Advisory Council
ARTG	Australian Register of Therapeutic Goods
CMEC Com	plementary Medicines Evaluation Committee
DMSO Di	methyl sulfoxide
ECCMHS	Expert Committee on Complementary Medicines in the Health System
FDA	Food and Drug Administration
IRCH International	Regulatory Cooperation for Herbal Medicines
NOEL	No Observed Effect Level
OCM	Office of Complementary Medicines
TCM Traditional	Chinese Medicine
TGA Therapeutic	Goods Administration
WHO	World Health Organisation

The Complementary Medicines Evaluation Committee (CMEC) held its sixty-fourth meeting in the Botany Room, Stamford Hotel Sydney Airport, Sydney, from 9.40 a.m. to 3.35 p.m. on Friday 14th December 2007.

Members of CMEC present were:

Professor Tony Smith (Chair)
Professor Alan Bensoussan
Dr Vicki Kotsirilos (morning session)
Associate Professor Douglas Moore
Professor Stephen Myers
Mr Kevin Ryan
Professor Gillian Shenfield
Professor Bill Webster
Associate Professor Heather Yeatman

Present from the Therapeutic Goods Administration (TGA) were:

Professor David Briggs
Dr Andrea Hinschen
Ms Michelle McLaughlin
Mrs Diane Wilkinson

1 PROCEDURAL MATTERS

1.1 Opening of Meeting

The Chair opened the meeting at 9.40 am and welcomed CMEC Members and TGA staff.

1.2 Apologies

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 63 (12 OCTOBER 2007)

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

Members made the following recommendation:

Recommendation 64.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 63, 12 October 2007), 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 JOINT AUSTRALIAN / NEW ZEALAND THERAPEUTIC PRODUCTS AGENCY MATTERS

CMEC did not consider any matters under this agenda item.

5 ACTION ARISING FROM PREVIOUS MEETINGS

5.1 'Arabinogalactan' derived from *Larix occidentalis* or *Larix larcinia*

Background

A TGA Officer introduced this item, advising Members of a new substance application for the use of larch arabinogalactan, as an ingredient in Listed medicines.

Members were advised that, as a therapeutic ingredient, larch arabinogalactan may be taken in a capsule form, and as a powder it can be added to food or beverages, with different proposed daily doses for each of four grades. The maximum recommended daily dose is 20 g/day (in 3 doses) for the purest form (>90% purity).

In a 3-week human study, hyperglycemia and hyperinsulinemia have been observed following dosing at 30 g/day. However it was importantly noted that, when given at 15 g/day, arabinogalactan was well tolerated, without these effects. Furthermore, when given at 8.4 g/day for 6 months, no apparent safety concerns were identified. The only adverse effects observed in clinical studies, aside from those for 30 g dose, were bloating and flatulence.

Outstanding chemistry and manufacturing issues, including a description of analytical testing methodology and a reduction in the cadmium levels, are currently being resolved. However, no further data which would have addressed the potential for arabinogalactan to induce hyperglycaemia, when given at higher doses, was provided. Nor is the raw experimental data on which Robinson's published paper was based, reporting this effect, made available.

Overall, pre-clinical and clinical data suggest that the oral use of two high grades of arabinogalactan as an ingredient of Listed medicines should be safe, subject to a yet to be established daily dose limit. The safety of larch arabinogalactan is also supported by its apparently extensive use as a food additive in many countries, including Australia.

CMEC was asked to advise whether or not arabinogalactan, derived from specific *Larix* species (*L. occidentalis* and *L. larcinia*), is suitable for use as an ingredient in Listed medicines, and if so, should its use be subject to any dose restriction and/or label advisory statement to assure its safety-in-use.

Discussion

Quality issues

Committee concerns pertaining to the "gap" of unidentified constituents present, to varying degrees, in the different purity grades of arabinogalactan were discussed.

Members were in favour of limiting arabinogalactan to higher grades only.

Members discussed the lack of a satisfactory method to distinguish between the upper grades of arabinogalactan and the need to develop a new analytical method to determine polysaccharide content and properly characterise the substance.

Overall, Members considered that if there is a method in place to distinguish between the various arabinogalactan grades, then this issue could be resolved.

Dose Limit

Members then considered whether a dose limit may be appropriate to allay the hyperglycemia and hyperinsulinemia concerns associated with 30 g/day arabinogalactan. While one Member expressed concern with setting a dose limit based on unverified data, another Member indicated that the TGA had already requested this information, and that no raw data was provided in the Masters thesis source from which the Robinson's paper was derived.

Members discussed whether a maximum daily dose limit of 15 g/day may be appropriate given this dose appeared to have no hyperglycaemic effect, and noted that while not statistically significant, there was still an elevation in blood glucose at this lower dose. In this respect, there may be insufficient data to determine a safe cut-off dose.

A Member highlighted arabinogalactan's long traditional food use, noting that there are no controls for this substance as a food. However, Members agreed that intake would likely be limited by the volume of food consumed.

Several Members were supportive of a dose limit of less than 15 g/day (such as 12 g/day), but were unclear as to whether this lower dose would be efficacious. In this respect, Members considered that any dose limit set would still need to be above a minimum therapeutically effective dose. In the absence of any further (i.e. efficacy) information, Members, with one exception, agreed that a maximum daily dose limit should be set at 15 g/day.

Overall, Members, with one exception, agreed that subject to the development of an appropriate assay to distinguish grades of polysaccharide purity and a compositional monograph, and standardisation of the preparation, there would be no major quality concerns for the higher grade arabinogalactan products. Members considered that animal toxicology studies raised no real issues of concern, however noted that it was sometimes unclear what substances were actually examined in these studies. Members remained concerned with the Robinson *et al.* study which suggested a very clear hyperglycaemic effect at 30 g/day. However, it was also noted that a long term lower dose study was not associated with any blood glucose alterations. Thus, a maximum dose limit of 15 g/day arabinogalactan was set to allay these hyperglycaemia concerns, without impacting upon therapeutic effect.

Members, with one exception, made the following recommendation:

Recommendation 64.2

CMEC recommends to the TGA that 'arabinogalactan' derived from *Larix occidentalis* or *Larix larcinia*, and being of "high-grade" purity (polysaccharide content ≥85%), is suitable as an ingredient in Listed medicines, subject to a maximum daily dose limit of 15 g, and resolution of outstanding composition issues.

5.2 Piperine (of *Piper nigrum* or *Piper longum*)

Background

At CMEC 63 (October 2007), a review of the safety of piperine, a component of the herbal species *Piper nigrum* and *Piper longum,* was initially considered.

Herbs and herbal preparations of pepper (*P. nigrum* and *P. longum*) that contain piperine as a component are permitted as ingredients in Listed medicines. However, as a single chemical

entity, piperine *per se* is not considered to meet the definition of a 'herbal substance' and is therefore not eligible for inclusion in Listed products.

Members were reminded that the CMEC 63 safety review of piperine was instigated by the TGA after a Listed medicine was identified to contain an ingredient with 98% piperine. Evidence presented in the safety review indicated that piperine can affect absorption and metabolism, and therefore oral bioavailability, of some medicines.

At CMEC 63, Members requested clarification of the estimates of daily dietary piperine intake, and how dietary intake compares to the potential doses available from Listed medicines. Members requested that the OCM review dietary piperine intake, and source, where possible, information surrounding the piperine content of products containing *P. nigrum* and/or *P. longum* on the Australian Register of Therapeutic Goods (ARTG).

At CMEC 64, Members were advised that, extrapolating from the limited consumption data available, the TGA estimates that the consumption of piperine per person per day in New Zealand is approximately 25 mg (presumably comparable to Australia), in the USA approximately 60 mg, and in India approximately 120 mg.

Members were also informed that the TGA had requested information (regarding the piperine content of their medicines) from sponsors of medicines containing *P. nigrum* and/or *P. longum* as an ingredient.

Currently, the ARTG has five Listed medicines (involving four sponsors) containing preparations of *P. longum* as an ingredient. The TGA has received information relating to 4 of these products, for which the content of piperine was stated to be 0.21%, or not known.

The ARTG has 39 Listed medicines that contain preparations of *P. nigrum*. Of these, 23 medicines have been identified by the TGA as possibly containing piperine. The TGA has received the following information regarding 21 of these 23 medicines:

- Where known, the piperine content ranges from negligible to 110 mg/unit dose.
- Three medicines contain extracts containing more than 95% piperine.
- Five medicines contain extracts containing 20-50% piperine.

Members were reminded that piperine has been shown to be rapidly absorbed, with an elimination half-life of approximately 2.5 hours. As piperine has a short half-life, a possible regulatory option proposed for Members consideration was to include a label statement advising that the medicine should not be taken concurrently with other medication.

The TGA Officer advised Members that currently reviewed evidence has suggested that, in the absence of dose-response studies for interactions between piperine and each ingredient at a specific dose, a safe maximum (and potentially therapeutically useful) dose of the alkaloid cannot be reliably determined.

However, based on the No Observed Effect Level (NOEL) value, and using a safety factor of 100 (accounting for interspecies differences and for differences in sensitivity between humans), the safe daily intake of piperine (as a component of pepper) was extrapolated to not more than 0.2 mg/kg, corresponding to 10 mg/day for a person with 50 kg bodyweight.

The Officer commented that it is likely that a typical daily dietary intake of piperine (as a component of pepper), as part of a Western diet, is around 25 mg, although much higher intakes are possible from spice-rich diets. It is, therefore, not unreasonable to assume that a 50% increase in the total daily intake of piperine from a therapeutic product would not markedly enhance the bioavailability of most chemicals that are sensitive to piperine's

actions. However, it was acknowledged that this assumption neglects the potential for multiple units or multiple products, each formulated with a limited amount of piperine, to be taken concomitantly, resulting in a delivery of a relatively high dose of piperine, an/or concomitant dietary intake of pepper.

Members were asked to advise the TGA if any regulatory action should be taken to control the use of piperine in Listed Medicines.

Discussion

Clarification of the safety concern regarding piperine

A TGA Officer reminded Members that there was no identified safety concern regarding piperine *per se*, and that the safety concern primarily relates to the substance's ability to increase the bioavailability of other substances, similar to the substance DMSO (dimethyl sulfoxide), which increases transdermal absorption of medications.

A Member commented that the central issue is not one of inherent toxicity, but the risk of inadvertent interaction with prescription or other medications, and that this effect could not be predicted, particularly with respect to this category of essentially unevaluated products.

Members discussed whether piperine is considered to be a therapeutic product, noting that while piperine is a component of the herbs *P. nigrum* and *P. longum*, preparations of which are permitted in Listed medicines, products containing purified piperine would currently be required to be Registered. Members then discussed whether isolated piperine has the same effect on bioavailability as piperine when present as a component of a herb. They concluded that in the absence of data to the contrary, the assumption would need to be made that it does.

Activity of piperine

A Member noted that whilst there was limited pharmacokinetic information available, there was evidence that piperine exerted bio-enhancement properties for 2.5 to 3 hours after consumption.

Another Member stated that there are several mechanisms by which piperine increases bioavailability, such as an action on CYP enzymes or increasing membrane fluidity.

The Member considered that some of these actions may elicit a large response, while others are much less. However, the fact that the effect on enzyme activity may last substantially longer than the substance's half-life is of particular importance. In this respect, the Member considered that piperine was not suitable for inclusion in Listed medicines.

Label warning statement

A Member suggested that a logical approach to safety concerns may be to separate medicine doses (i.e. not take prescription medicines at the same time as a supplement containing piperine). The Member stated that this would not be unlike the warning given for the substance cholesterin, which should not taken with warfarin or digoxin due to the substance's binding abilities.

However, another Member expressed concern that a label warning statement advising separation of medications, does not take into account the different mechanisms by which piperine increases bioavailability.

A TGA officer also agreed that a label warning was unlikely to address the main issues surrounding the use of piperine, and may be difficult to implement in the absence of data relating to which other ingredients it may interact with.

Maximum dose limit

Members discussed controlling safety-in-use of piperine (as a component of Listable Piper species) *via* a maximum dose limit (either a daily dose or a unit dose), noting that while it may not be practical to restrict piperine when it is widely consumed in the diet, any cut-off figure should be comparable to the amount an individual would obtain from dietary pepper.

One Member proposed that, as most products contain less than 30 mg piperine (as a component of Piper species), a cut-off figure of 20 mg may be reasonable. However, another Member commented that a supplement containing 20 mg piperine had demonstrated a significant clinical effect on phenytoin levels, therefore any limit should be as low as possible. The Member suggested a 10 mg cut-off limit.

Members agreed that a cut-off dose of 10 mg in oral medicines could be justified based on toxicological principles. Members then discussed whether this cut-off dose limit should be on a per unit dose or per daily dose basis, agreeing that as NOELs are based on daily doses and not unit doses, the cut-off, if based on the NOEL, should be based on a daily cut-off dose limit.

Overall, Members agreed that a daily dose limit of 10 mg piperine was an appropriate regulatory control on the use of piperine as a herbal component in Listed medicines.

Members made the following recommendation:

Recommendation 64.3

CMEC recommends to the TGA that a maximum daily dose limit of 10 mg be adopted for piperine when present as a component in herbal preparations for use in Listed medicines.

5.3 Hepatotoxicity guidance document

Background

A TGA Officer introduced this item, reminding Members that at CMEC 61 (April 2007), whilst considering an appropriate recommendation in relation to a report of hepatotoxicity associated with a herbal medicine, Members suggested that a guideline or checklist might be useful as an 'in house' tool to ensure a measured and consistent approach to addressing reports of hepatic injury associated with the use of herbal or complementary medicines.

At CMEC 62 (June 2007), the Committee was asked to comment on the approach proposed by the OCM to ensure consistent processing of adverse reports of hepatotoxicity associated with the use of herbal preparations and products. The CMEC agreed on the process and the approach proposed by the OCM, with minor amendments, and recommended that this be formulated into a guidance document.

Members were asked to comment on, and endorse if appropriate, the Draft Guidelines for assessing reports of hepatotoxicity associated with the use of herbal medicinal products.

Discussion

Members unanimously commended and endorsed the draft guidance document. They considered that while it could not realistically provide all the answers to address the complex issues surrounding herbal associated hepatotoxicity, it appeared to incorporate all appropriate

literature and classifications, and formally documented some of the work the TGA does as a matter of course.

While some Members considered that the steps identified in the guideline would normally be undertaken by the OCM in any case, they were glad that this process was being formalised into a guidance document and suggested that a checklist could also be developed to complement the guideline.

Members also requested that the document be forwarded onto a named expert in hepatotoxicity for comment.

Overall, CMEC endorsed the *Draft Guidelines for assessing reports of hepatotoxicity associated with the use of herbal medicinal products*, with minor amendments.

6 EVALUATION OF NEW SUBSTANCES

CMEC did not consider any matters under this agenda item.

7 SAFETY OR EFFICACY REVIEWS

7.1.1 International Regulatory Cooperation for Herbal medicines (IRCH) Overview

A TGA Officer introduced this item, highlighting the fact that while the use of herbal medicines has increased globally, the regulatory status of herbal medicines varies greatly from country to country.

Members were advised that many of the challenges experienced for herbal medicines relate to the lack of quality research data, the lack of appropriate control mechanisms, the lack of education and training of providers, and the lack of expertise.

Members were informed that the World Health Organisation (WHO) was tasked with providing support on the provision of information sharing on regulatory issues and databases, organising training workshops on the regulation of herbal medicines, herbal medicine safety monitoring, and supporting the provision of technical guidelines on research and evaluation of herbal medicines.

To this end, following an initial workshop in Canada in November 2005, the International Regulatory Cooperation for Herbal medicines (IRCH) was established.

Members were advised that there are currently 19 member countries of the IRCH (of which Australia is one), as well as a number of observer countries and regional bodies.

Members were informed that the IRCH share information on technical matters related to regulation of herbal medicines via an electronic, web-based communication system (WHO MedNet), on a daily basis (as required), through an Information Focal Point nominated by each Member country of IRCH.

The IRCH also convene annual meetings, the first of which was held in Beijing, China, in October 2006, and the second was held in Kuala Lumpur, Malaysia, in July 2007.

Members noted that at the most recent meeting, a number of priority problems and issues were identified. Of particular relevance to CMEC is that the OCM now has access, via the WHO MedNet, to regulators of herbal medicines in any IRCH member country. This system allows easy and effective dialogue between members, either on an individual or group basis,

which has allowed the OCM to obtain relevant information in relation to the way that herbs are regulated in these countries, and any safety concerns that may exist.

The Officer pointed out that while the OCM may not necessarily receive responses from all of the participating countries, those responses received are usually indicative of potential problems with a particular herbal substance.

Members were advised that the TGA intends to post any herbal safety reviews undertaken by the OCM, in order to facilitate knowledge-sharing within this group.

CMEC noted the establishment of an IRCH, acknowledging both the interest of this group in efficacy (in addition to quality and safety), and the opportunities it presents for participating countries to learn from one another.

7.1.2 Review of *Convolvulus arvensis*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern has been identified with respect to the use of all plant parts of the herb *Convolvulus arvensis*. The whole plant appears to contain a mixture of mostly tropane alkaloids, pyrrolidine alkaloids, and proteoglycans.

Members were advised that there are currently only two products listed on the ARTG containing *C. arvensis,* among other ingredients. One of these products contains the herb as an excipient only, and the other product contains the seed powder. Both products are indicated for use in constipation.

The current TGA review has revealed that there is limited available information on traditional uses of *C. arvensis,* and its use as such, does not appear to be widespread. Most of the available literature focuses on the plants status as a highly invasive, widespread, noxious weed. However, it seems that traditionally the roots and aerial parts have been used, most commonly as a purgative. No information could be found on traditional use of the seeds and none of the traditional literature references indicated any recommended dosage for *C. arvensis.*

Members noted that animal studies show that relatively high oral doses of *C. arvensis* may be potentially toxic, and that occasional ingestion of the aerial parts can produce mild inflammatory effects on the stomach and liver.

Members were also informed that it appears evident that *C. arvensis* affects gastrointestinal motility, but that the extent of this is not fully understood, particularly in humans, as there are no human studies. The available literature suggests that the constituents of *C. arvensis* decrease intestinal motility (despite possibly causing sharp contractions initially), which appears inconsistent with its use as a therapeutic agent in the management of constipation.

The current review has not located any reports of adverse events reported for the herb in the ADRU database, or in literature reports.

Members were asked to consider if any regulatory action may be required, and if so what type, to control the use of *C. arvensis* L. as an ingredient in Listed medicines.

Discussion

A TGA officer stated that whilst there is limited data available, many modern herbalists express unease regarding the use of this herb. A CMEC Member also expressed their

discomfort with respect to the use of this herb, adding that as the herb is not in widespread use, and it is not substantially consumed or prescribed, any proposed regulatory action would not have a significant impact.

Another Member considered the herb to be toxic and did not support its continued use in Listed Medicines. Moreover, they pointed out that *C. arvensis* is not included in the *Chinese Herbal Materia Medica*.

A TGA Officer advised that the herb is included in the *Homoeopathic Pharmacopeia of the United States* as a valid homoeopathic monograph.

Toxicology

One Member pointed out that there were only two relevant publications examining the toxicity of *C. arvensis*. In one paper, toxic effects were seen in horses grazing in *C. arvensis*-infested areas. In the other paper, mice consuming up to 1.5 g/day of *C. arvensis* leaves died or were sacrificed moribund 4-5 days later, with gastritis and/or hepatitis reported at necropsy.

In a further study, rats given 0.5 to 1 g/day of fresh *C. arvensis* demonstrated inhibited hepatic Phase 1 drug metabolising enzyme activity.

The Member further remarked that the alkaloids present in the herb are toxic, but since the dose used in the study was 1 g, which they considered a very large dose, the relevance of this to humans is unclear, other than the obvious conclusion that if you consume enough of the substance it will result in death.

Medicines in the ARTG

A Member also pointed out that the medicines included in the ARTG are grandfathered, and subsequently are generally not well-characterised, with no information available regarding possible adulteration or substitution.

Another Member remarked that of the two medicines included in the ARTG, one included the ingredient as an excipient, and the Member questioned the use of the herb in such a role.

Overall, Members considered that in the absence of supporting data to the contrary, the herb did not appear to be suitable for inclusion as an ingredient in Listed Medicines.

Members made the following recommendation:

Recommendation 64.4

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

7.1.3 Review of *Periploca sepium*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern has been identified with respect to the presence of cardiac glycosides in the herb *Periploca sepium*.

As an aside, the Officer pointed out that whilst other species of *Periploca* have also been identified as containing cardiac glycosides, only *P. sepium* is currently eligible for inclusion in Listed Medicines (currently with no restriction on use).

Members were advised that there are currently only two medicines Listed in the ARTG that contain *P. sepium* as an ingredient, in small quantities. Both products also contain *Carthamus tinctorius* flower.

Members noted that the root bark of *P. sepium* appears to be the part used traditionally and the indications for the herb include rheumatic arthritis, cardiac palpitations, shortness of breath and oedema of the lower extremities. General adverse reactions to *P. sepium* are reported to include nausea, vomiting and diarrhoea, but these mostly disappear after reduction of the dose or discontinuation of the drug. High doses lead to bradycardia, generalised tremor followed by paralysis, cardiac intoxication and in severe cases, death.

P. sepium is reported to have been used in China and other countries as a cheaper substitute for the herbs *Eleutherococcus senticosus* and *Acanthopanax gracilistylus*, and has resulted in adverse reactions.

Members were informed that the normal dosage of the herb is reported to be 3-6 g. The toxic dose is considered to be approximately 10-15 g, administered singly as a decoction.

The stem bark, root bark and stem of *P. sepium* are known to contain cardiac glycosides, the principle of which is 'periplocin'. Periplocin is a 'digitalis-like compound', which when taken at an appropriate dose level will cause cardiovascular toxicity, and can affect the neuronal and gastrointestinal systems. 'Digitalis glycosides' such as digoxin are used therapeutically to improve heart performance by increasing the force of contraction of the heart, and have a narrow therapeutic index. The 'digitalis glycoside' yield of *P. sepium* is comparable to the yield contained in the herb *Digitalis lanata.* However, the Traditional Chinese Medicine (TCM) dose for *Digitalis lanata* is 15 times lower than that for *P. sepium*, possibly in recognition of far greater toxicity of digoxin compared with periplocin, considering that the glycoside content of each herb is comparable.

Members were asked to consider if any regulatory action may be required, and if so, what type, to control the use of *P. sepium* as an ingredient in Listed medicines.

Discussion

A Member pointed out that *P. sepium* contains digitalis glycosides, which, if given in a high enough dose, will result in death.

Another Member advised that the toxic dose of the herbal substance is only twice the therapeutic dose, and that the herb is considered toxic in TCM. The Member also added that there are a number of other, less toxic, herbal substances that could be used as good substitutes for the herb medicinally.

Members agreed unanimously that the herb was not considered to be low risk, and therefore should not remain eligible for inclusion in Listed Medicines.

Members made the following recommendation:

Recommendation 64.5

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

7.1.4 Review of *Pinellia ternata*

Background

A TGA Officer introduced this item, advising Members that a potential safety concern has been identified with respect to the use of the raw seed and possibly other plant parts of the herb *Pinellia ternata.*

Members were also reminded that at CMEC 63, the Committee was advised of an adverse event attributed to *P. ternata*, which involved a 37-old man who suffered acute hepatitis and jaundice after consumption of multi-herbal formula containing *P. ternata* as one ingredient. However, the current TGA review was not able to locate any other liver-related adverse events implicating P. *ternata.*

Members were advised that *P. ternata* is currently permitted as an ingredient in Listed medicines, with no restrictions on its use. There are 154 Listed medicines in the ARTG containing this ingredient. Most of these medicines contain the root, tuber or rhizome of the herb. However, one medicine lists 'fruit', one medicine lists 'stolon' and another medicine lists 'leaf' as the plant part used.

Members were informed that the tuber of *P. ternata* is the plant part used traditionally and has a long history of use in China, Japan and Korea. The main therapeutic use for the herb is for conditions associated with excessive phlegm.

Traditionally, the raw herb is considered toxic and is used for external treatment only. For internal use, the herb is pre-treated to reduce the toxic components. Ingestion of the unprocessed drug or over dosage of the prepared drug is reported to cause severe irritation of the mucous membrane of the mouth, pharynx and gastrointestinal tract, and toxic effects on the nervous system.

Members noted that the US Food and Drug Administration (FDA) include *P. ternata* on the banned substance list as a plant source of ephedrine alkaloids. However, this review has not confirmed the FDA's finding. If these alkaloids are present in the herb, it appears to be only in minute amounts.

A component of the herb, the protein pinellin, has been purported to have abortifacient properties. Traditional preparations of *P. ternata*, where the herb is pre-treated with alum solution, ginger, lime water, or decocted, are purported to destroy this protein.

Other components (such as alkaloids, phenols and calcium oxalate) are known to irritate the mucous membranes of the gastrointestinal tract. Certain preparation methods (such as cooking, drying and decocting) are purported to destroy these mucous membrane irritating components.

The herb is considered an effective treatment in TCM, with a long history of use in China, Japan and Korea, and is also included in a large number of Listed medicines in Australia. Therefore, any decision on the suitability of the ingredient, or a component thereof, in Listed Medicines should also address issues to manage the impact such a regulatory decision may have, both within Australia and internationally.

Members were asked to provide advice to the TGA on whether the current unlimited use of *P. ternata* in Listed medicines presents an unacceptable safety risk due to the substance's known toxic properties. Members were also asked to consider whether restriction of the ingredient to pre-treated material, or a restriction on the component, pinellin, in the ingredient, might

provide assurance of its safe use, and whether the long history of use with few reported side effects (when used appropriately) provide assurance of safe use in Listed Medicines.

Discussion

The Chair pointed out that this herb was different to the previous two herbs considered at CMEC 64 as this herb has a relatively well established history of traditional use.

Traditional use

A Member advised that *P. ternata* is widely used in TCM to remove fluid from the stomach and intestine. This Member also emphasised that there was an important distinction regarding the raw herb and the prepared herb. In TCM, only the prepared herb is used therapeutically. When queried whether the herb was used only under practitioner supervision, the Member advised that in most cases the herb would be managed under practitioner supervision, and there was unlikely to be much 'self prescription' of the herb. However, as *P. ternata* is permitted in Listed medicines, it is currently legally available for self administration as any herbal preparation.

Members discussed whether incorporation in a traditional formulation had any impact on the safety of *P. ternata*. They noted that this herb is often used in combination with ginger. A Member added that there are no particular traditional warnings regarding pregnancy. Members further noted that preparations of *P. ternata* are contained in 154 products, in amounts that do not appear to be a cause for concern.

Abortifacient activity

One Member commented that *P. ternata* had some purported abortifacient activity, but that a study in rats, demonstrated conflicting results. At a dose of 9 g/kg, the pregnancy rate was 44% (56% not pregnant), whilst at a higher dose of 30 g/kg, the pregnancy rate was 81% (29% not pregnant). The Member also stated that while the prepared decoction did result in foetal loss, 30 g/kg was considered an extremely high dose. Another Member also pointed out that this particular dose related to the raw tuber.

Members unanimously agreed that preparations of the raw tuber of *P. ternata* are not suitable for use in Listed medicines, and that only preparations of pre-treated tubers remain suitable for such use.

Members made the following recommendation:

Recommendation 64.6.1

CMEC recommends to the TGA that untreated raw tuber of *Pinellia ternata* is not suitable for use in Listed medicines.

Recommendation 64.6.2

CMEC recommends to the TGA that traditional preparations of the tuber of *Pinellia ternata* remain suitable for use in Listed medicines.

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) Meetings 302 & 303

Members noted the adverse drug reaction reports involving complementary medicines from the 302nd and 303rd meetings of ADRAC.

Complementary medicine issues

CMEC discussed complementary medicine issues of interest from meeting 302.

Case reports

Members discussed current case reports in detail from both meetings.

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 Practitioner access to complementary medicines

A TGA Officer introduced this item, reminding Members that at CMEC62 (June 2007), the Committee discussed the difficulties that practitioners sometimes experience in relation to access to legitimate 'tools of trade'. Members agreed that this situation was complicated by the fact that medicines are regulated on a federal basis, whilst practitioners are the responsibility of states and territories.

Members noted Recommendation 18 of the Expert Committee on Complementary Medicines in the Health System (ECCMHS), which advocates that:

"*The Australian Health Ministers' Advisory Council (AHMAC) be urged to promote early implementation across jurisdictions of a uniform approach to the legislation that regulates access to and use of medicines*."

Members also noted the difficulties in relation to implementing regulation for diverse complementary medicine practitioner groups, and that resolution of this matter is likely to be imperative prior to permitting complementary medicine practitioners access to specific medicines.

Members were advised that this matter was considered by the TGA and Medsafe as part of the development of a joint regulatory scheme between Australia and New Zealand.

Key issues identified included:

- current practitioner access to manufactured products;
- issues in relation to the 'cachet' associated with the term 'practitioner only', and related marketing/access implications;
- appropriate regulation of complementary medicine practitioners;
- the need for maintenance of appropriate quality standards;
- traceability of products/ingredients;
- equity of supply in the market place;
- safety of ingredients/products which have not been established; and
- implications of such safety concerns on the broader industry.

CMEC noted the issues that arise when considering regulatory provisions to potentially permit wider practitioner access to complementary medicines.

11.2

CMEC considered one matter under this agenda item.

12 SPONSOR REPRESENTATIONS TO CMEC

CMEC did not consider any matters under this agenda item.

13 OTHER BUSINESS

CMEC did not consider any matters under this agenda item.

14 RECOMMENDATION RECORD

Item 2 Confirmation of Draft Minutes of CMEC 63 (12 October 2007)

Recommendation 64.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 63, 12 October 2007), as amended, are a true and accurate record of that meeting.

Item 5.1 'Arabinogalactan' derived from *Larix occidentalis* or *Larix larcinia*

Recommendation 64.2

CMEC recommends to the TGA that 'arabinogalactan' derived from *Larix occidentalis* or *Larix larcinia*, and being of "high-grade" purity (polysaccharide content ≥85%), is suitable as an ingredient in Listed therapeutic products, subject to a maximum daily dose limit of 15 g, and resolution of outstanding composition issues.

Item 5.2 Piperine (of *Piper nigrum* or *Piper longum*)

Recommendation 64.3

CMEC recommends to the TGA that a maximum daily dose limit of 10 mg be adopted for piperine when present as a component in herbal preparations for use in Listed medicines.

Item 7.1.2 Review of *Convolvulus arvensis*

Recommendation 64.4

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

Item 7.1.3 Review of *Periploca sepium*

Recommendation 64.5

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

Item 7.1.4 Review of *Pinellia ternata*

Recommendation 64.6.1

CMEC recommends to the TGA that untreated raw tuber of *Pinellia ternata* is not suitable for use in Listed medicines.

Recommendation 64.6.2

CMEC recommends to the TGA that traditional preparations of the tuber of *Pinellia ternata* remain suitable for use in Listed medicines.

The Chair closed the meeting at 3:35 pm.