TGA THERAPEUTIC GOODS ADMINISTRATION

Commonwealth Department of Health and Ageing

CMEC 41 Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Forty-first Meeting
1 August 2003

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
BSE	Bovine spongiform encephalopathy
CHC	Complementary Healthcare Council of Australia
CK	Creatine kinase
CPK	Creatine phosphokinase
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-first meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in the Wangaratta Room at the Hilton Melbourne Airport, 9.30 am to 4.30 pm on Friday 1 August 2003.

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
Professor Bill Webster
Dr Iggy Soosay

Present from the Therapeutic Goods Administration (TGA) were:

Dr Fiona Cumming
Dr John Hall
Dr David Briggs
Dr John McEwan
Dr Richard Hill
Mrs Michelle McLaughlin

Other attendees
Dr Duncan Topliss (Chair of ADRAC)
Dr Richard Whiting (Chair of MEC) (Present for morning session from 9.50am)

1. Procedural Matters

1.1 Opening of Meeting

The Chair opened the meeting at 9.32 am and welcomed CMEC Members, TGA staff, and visitors Dr Duncan Topliss (Chair of ADRAC) and Dr. Richard Whiting (Chair of MEC).

1.2 Apologies

The CMEC Secretariat received apologies from Associate Professor Heather Yeatman.

1.3 Conflict of Interest

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

Members were reminded that the annual declaration of conflict of interest falls due at this meeting, and the importance of this document was reiterated. Members were requested to complete and supply to the OCM the annual conflict of interest declarations within a few days of the meeting.

2. Confirmation of Minutes of CMEC 40 (30 May 2003)

The minutes of the fortieth meeting of the CMEC were accepted as an accurate record of proceedings without amendment.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 41.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 40, 30 May 2003) 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)

No matters were considered under this agenda item.

4. CMEC Working Party on Herbal Medicine Issues

No matters were considered under this agenda item.

5. Action Arising from Previous Meetings

No matters were considered under this agenda item.

6.1 Evaluation of New Substances

The Committee deferred consideration of one matter under this item to the next meeting of the CMEC (September 2003)

7.1 Safety or Efficacy Review: Kava

Background
A TGA Officer introduced this item, reminding Members that both CMEC and ADRAC had been involved in discussions regarding kava (*Piper methysticum*) since 2001, following mounting international concerns over reports of hepatotoxicity associated with the herb. In July 2002, the TGA initiated a proposal to cancel kava-containing medicines after the death, from complications of liver failure, of an Australian woman who had been taking a kava-containing product.

A voluntary recall of kava-containing products was undertaken in conjunction with the complementary medicines industry, and in 2003 the TGA organised an expert committee – the Kava Evaluation Group (KEG) – to review the safety of kava-containing medicines. This group included membership from both sides of Tasman, and met on 30th June 2003 to review the safety data available for kava and to make a recommendation to the CMEC on whether or not kava is suitable for use as an ingredient in listed medicines.

Members were asked to note that the efficacy of kava was not investigated as part of the safety review, and clinical studies were only evaluated in the context of safety.

In conducting a comprehensive safety review of data, the TGA received a number of public submissions from interested parties. Recommendations for future regulation of kava from these submissions included the following proposals:

- Further warning statements on the label;
- That kava should only be available via a practitioner consultation; and
- That a limit be placed on the concentration of the kavalactones.

The KEG examined different forms of kava that had been associated with adverse reactions internationally, and noted that it was very difficult to find any clear association between the hepatotoxicity, severity of the adverse event, dose, age or sex of the patient and the particular preparation of kava involved. There was a trend in that the extracts involved were generally made using an organic solvent, but there was little specific detail about the products. There were also some limitations in terms of the details in the individual adverse reaction reports.

One important item of information provided for consideration, albeit an unpublished and preliminary study undertaken at the Australian Centre for Complementary Medicine Education and Research, involved *in vitro* tests using two liver cell lines which looked at potential hepatotoxicity of different kava extracts. Initial results in the *in vitro* model suggested that there may be an association between hepatotoxicity, and different degrees of polarity of the extraction solvent.

The key findings from the TGA safety review of kava, which was submitted to the KEG, were:

- Evaluations of reported case studies indicate that there is a possibility of a causal relationship between hepatotoxicity and kava-containing products;
- Currently, it is not possible to predict which kava-containing products may be at risk of causing hepatotoxicity, or who may be at risk of hepatotoxicity following ingesting of certain kava-containing products; and
- While published studies do not clearly demonstrate the hepatotoxicity of kava, there is not sufficient evidence to eliminate certain kava-containing products as being hepatotoxic.

The KEG made six recommendations regarding the regulation of kava-containing medicines. These recommendations were provided to the CMEC for consideration. Members noted that if the CMEC recommendations differed from those proposed by the KEG, both sets of recommendations would be presented to the TGA.

Present discussion
Members discussed the working of the Kava Evaluation Group and its recommendations, and noted that a number of kavalactones are potentially hepatotoxic at high concentrations.
Of particular note was that traditional preparations of kava seem to be significantly safer than the newer extracts now available. Members noted that in traditional usage of kava, only the whole or peeled root is used.

CMEC Members discussed the first recommendation proposed by the KEG (see below). Members noted that the traditional preparation of kava is where the root is pounded or powdered and dispersed through water. In comparison, a water extract involves separation of the aqueous phase from the root residue. A Member queried whether children should be included among those for whom use of kava was not recommended (Recommendation 1 below). Members were reminded that this matter had been previously debated by the CMEC (CMEC4, April 1998), and noted that a warning against use in children under 12 years old was not required.

Members of CMEC discussed the effects of water temperature on kava extraction, and noted that there was not enough information to determine the effects of hot or cold extraction. A Member communicated the preliminary finding that as kava was extracted across a polarity scale, there was not only an increase in total kavalactone extraction, there appeared also to be a selective and disproportionate extraction of kavalactones with the greatest toxicity.

Members discussed the impact of the kava recall on practitioner prescribing. Members noted that extemporaneous dispensing of kava was not covered by the initial voluntary recall, but while practitioners expressed concern that they had lost access to an important therapeutic agent, many had voluntarily ceased supply. KEG Recommendation 1 (below) was endorsed with one abstention.

Members discussed the second recommendation proposed by the KEG, involving homoeopathic preparations. Members were advised that discussion by KEG centred around the dilution of kava achieved by a 1000 fold dilution of a kava mother tincture, which is the current cut-off below which these medicines are generally exempt from the requirement to be Listed on the ARTG. A

Member commented that dose of the medicine may be an additional issue that should be considered when discussing the regulation of homoeopathic forms of restricted substances in the future, noting that homoeopathic products are often administered in very small amounts.

KEG Recommendations 2, 3 and 4 (below) were endorsed with no abstentions.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 41. 2

The CMEC endorses the following four recommendations made by the Kava Evaluation Group (KEG), and recommends to the TGA:

Recommendation 1

That:

(i) aqueous dispersions of whole or peeled rhizome of Piper methysticum;
(ii) aqueous extracts of whole or peeled rhizome of Piper methysticum; and
(iii) dried whole or peeled rhizome of Piper methysticum

are suitable for use as ingredients in Listed medicines for oral use, subject to the following conditions:

(a) the preparation does not contain, for its recommended daily dose, more than 250 mg of kavalactones; and
(b) if the preparation is in a tablet or capsule – the amount of kavalactones does not exceed 125mg for each tablet or capsule; and
(c) if the preparation is in a tea bag – the amount of dried whole or peeled rhizome does not exceed 3g for each tea bag; and
(d) if the preparation contains more than 25mg of kavalactones per dose – the label on the goods includes the following warnings (or words to the same effect):
- **Not for prolonged use. If symptoms persist, seek advice from a health-care practitioner;**
- **Not recommended for use by pregnant or lactating women; and**
- **May harm the liver.**

Recommendation 2

That *Piper methysticum* may be used in homoeopathic preparations more dilute that a one thousand fold dilution of a mother tincture.

Recommendation 3

That:

(i) aqueous dispersions of whole or peeled rhizome of *Piper methysticum;*
(ii) aqueous extracts of whole or peeled rhizome of *Piper methysticum*; and
(iii) dried whole or peeled rhizome of *Piper methysticum*

are suitable for use as ingredients in Listed medicines for topical application to the rectum, vagina and by spray to the throat.

Recommendation 4

That *Piper methysticum* may be used as an ingredient in Listed medicines for topical application to the skin.

Members discussed KEG Recommendation 5, which proposed that "ethanolic kava extracts of whole or peeled rhizome of *Piper methysticum* up to 25% ethanol in water, *may* be suitable as ingredients in Listed medicines for oral use. However, more data on the safety of these extracts are required before a decision about the use of these extracts as ingredients in Listed medicines for oral use can be made".

Members were advised that this recommendation was made by the KEG in recognition of the substantial discussion that centred on the issue of polarity of solvents and hepatotoxicity, and that it may be necessary to return to this issue if more data becomes available. Several Members indicated that they considered that the KEG recommendation was more appropriately regarded as a statement rather than a recommendation and CMEC resolved to note KEG Recommendation 5 rather than endorsing it outright.

Members discussed KEG Recommendation 6, and resolved to endorse the recommendation with an amendment to the original wording to avoid possible confusion about the safety of ethanol/water extracts of kava, consistent with the Committee's discussion relating to Recommendation 5 above.

CMEC Recommendation:
Members made the following recommendation with one abstention:

Recommendation 41.3

The CMEC recommends to the TGA that products containing *Piper methysticum* must be Registered prior to their supply, other than:

(i) aqueous dispersions of the whole or peeled rhizome of *Piper methysticum*;
(ii) aqueous extracts of whole or peeled rhizome of *Piper methysticum*;
(iii) dried, whole or peeled rhizome of *Piper methysticum*;
(iv) products for topical application to the skin; and
(v) homoeopathic preparations more dilute than a thousand fold dilution of a mother tincture.

Item 7.2 Safety review of *Chelidonium majus* (Greater Celandine)

Background
A TGA Officer introduced this item and indicated that at CMEC40 (May 2003), members first considered a preliminary safety review of the herb *Chelidonium majus* (greater celandine), which had been prepared by the OCM following a report in the *Lancet* of liver toxicity associated with the herb. At this meeting, the CMEC deferred making a recommendation on the need for any stronger controls over the availability of this herb – it is currently permitted as an ingredient in Listed medicines – until the TGA had fully completed the review of the safety profile of *C. majus*.

The report presented for CMEC consideration at this meeting provided a more comprehensive safety assessment of *C. majus*, including input from the German Federal Institute for Drugs and Medical Devices (BfArM). It also provided further details relating to the literature cases of liver toxicity reported in the preliminary safety assessment, and some other additional data. Much of the data had been presented in the preliminary safety assessment, although some had been further elucidated following access to the complete published paper.

Chelidonium has been studied for its effects on smooth muscle, on the liver (choleresis, hepatoprotection), and central nervous system, as well as for antiviral, anti-microbial and antitumor effects as detailed in the evaluation paper. It is traditionally used to treat conditions of the liver, and as many reported cases of hepatotoxicity associated with chelidonium appear to follow its use for liver problems, this confounding effect must be kept in mind.

Celandine herb has received a positive evaluation by the German Commission E for the treatment of spastic discomfort of the bile ducts and gastrointestinal tract at a stated dosage of 2-5g/herb/day, equivalent to 12-30mg total alkaloids (calculated as chelidonine). The alkaloids of *c. majus* appear to be central to both the reported activity of chelidonium, and to its reported hepatotoxic effects.

BfArM has provided the OCM with a copy of an unpublished report, written in 1999 in German, and conducted on behalf of the German industry, concerning the cytotoxicity in cultured rat cells of the alkaloids found in *C. majus*. It suggested that the amounts of individual alkaloids in a medicine, rather than the total alkaloid load, could underlie the hepatotoxicity of these products. However it was also noted that hepatocyte vacuolisation occurred with *C.* majus extracts and formulations *in* vitro, but not with the individual alkaloids. Whilst this study shows that these extracts were cytotoxic to rat liver cells *in vitro*, the mechanism is not known. Consideration must also be given to the contrasting studies that have looked into the *in vivo* hepatoprotective effects of chelidonium in rats.

Following consideration of this study, the German authorities drew the conclusion that preparations of *Chelidonii herba* have a negative benefit-risk-relation and "should enter the list of forbidden plants". However this regulatory viewpoint (determined *c*1999) does not appear to have been acted upon at this point in time, other than that the labelling of 12 single or multi-ingredient products currently available on the German market now contains a caution for hepatotoxic risk.

Details of hepatotoxic adverse reactions to chelidonium in Germany were provided to the OCM. In most cases the subjects were taking a number of different medications and some of these medicines have been known to product hepatotoxicity. However according to the causality rating system, *C. majus* was the sole suspected agent in the majority 52 of these cases.

It should be noted that causality has not been proven in the above cases, and there is a long history of apparent safe ingestion of this herb in European and Chinese herbal medicine. However, there does appear to be a definite link between the ingestion of chelidonium and moderate to severe acute, reversible hepatotoxicity (in a relatively small number of individuals given the total estimated intake). This link is supported in the additional information provided by an Australian hepatologist who agreed with the original Benninger paper, which concluded that the ten cases are consistent with hepatotoxicity and that the greater celandine was an appropriate candidate agent.

The mechanism underlying the hepatotoxic effect remains to be fully elucidated. However the available studies and the reports of adverse reactions appear to be consistent with idiosyncratic drug-induced hepatitis, and some findings appear to support a possible immunoallergic mechanism.

The German authorities indicated that the observed cases of hepatotoxic reactions in Germany could not be attributed to any particular preparation or extract of the herb, and there does not appear to be any dose dependency. As such, no predictions can be made regarding the potential hepatotoxicity of individual products. As reported in the previous review of *Chelidonium majus*, only herbal practitioners may use chelidonium in the UK, the herb is freely available in the USA, and there are 62 products currently included in the Australian Register of Therapeutic Goods (ARTG), seven of which are homoeopathic preparations.

Members were also reminded of a similar issue relating to liver toxicity associated with the use of the herb *Larrea tridentata* (chapparal), which was considered by the CMEC at its 38th meeting in November 2002. In this case, Members advised that chapparal should remain eligible for inclusion in Listed medicines, provided labels for oral products incorporated a warning advising consumers to use the product for a limited period of time, to seek advice from a healthcare professional and/or discontinue use if they have had, or develop, symptoms of liver disease.

CMEC was asked to consider the preliminary and final safety reviews of *Chelidonium majus* and to advise whether or not this herb should continue to be permitted for use as an ingredient in Listed medicines.

Present discussion.
A Member noted the similarity of this situation to that of chaparral, considered late last year, and expressed the opinion that the most appropriate action would be to treat this herb in the same manner. The question arose as to how long preparations containing this herb might be used, and a Member advised that it is usually incorporated into an acute rather than a chronic remedy, and would generally only be used for 4-6 weeks.

Members were advised of input from Germany, indicating that the traditional alkaloid load for chelidonium products used to be lower than at present and that evidence arose that this was not an effective dose. Subsequently there has been a trend over the last decade to increase alkaloid load. It is thus possible that the products associated with the hepatotoxicity contain a higher dose of alkaloids than were traditionally used, however there is no real documentary evidence supporting this. Another Member commented that the variable latency periods in the development of hepatotoxicity indicated that there was no clear link between use of the product and direct toxicity, and that idiosyncratic mechanisms are more likely.

Members discussed the options proposed by the TGA. A TGA Officer pointed out that whichever option was selected, given that chelidonium is commonly used in homoeopathic medicines, it may be necessary to consider alternative regulatory controls for homoeopathic preparations of *Chelidonium majus*.

A CMEC Member commented that should the Committee support retaining the herb for use in Listed medicines, they strongly recommended a warning that does not indicate a potential risk free usage period as was the case for chaparral.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 41.4

CMEC notes the safety review conducted by the TGA and recommends that the TGA maintain *Chelidonium majus* as an ingredient for use in Listed medicines, but with a warning statement to be included on the label of oral products. The statement is to advise consumers to use products containing the herb under the supervision of a healthcare practitioner, to caution consumers who have a history of liver disease, and to warn consumers to discontinue use of the herb if particular symptoms indicative of liver problems occur

The recommendation was passed, with 2 objections.

Item 7.3 Safety review of Chromium picolinate as a nutritional supplement

Background
A TGA Officer introduced this item, explaining that this review was based upon an original evaluation carried out by the United Kingdom's food regulator, the Food Safety Authority (FSA), in relation to the safety of a wide range of vitamin and mineral supplements. The aim of the review was to try and establish either safe upper limits, or guidance levels, for these substances.

The findings of this British review in relation to the use of chromium as a nutritional supplement, in particular chromium (III) picolinate (CrPic), were identified by the OCM as being of

significant concern. The FSA review recommended that, although there are insufficient data from human or animal studies to deliver a Safe Upper Limit for chromium, the use of trivalent chromium was not expected to produce adverse effects at daily doses up to 0.15mg/kg/day or 10mg/person/day. This dose is considered to be quite large, with average intake internationally estimated at approximately 25-35µg/day. However, this recommendation excluded one form of trivalent chromium, the organic salt – chromium picolinate (CrPic), which unlike other forms of trivalent chromium was shown to cause DNA damage in mammalian cells *in vitro*.

One particular study looked at *in vitro* evaluation for mutagenicity, using Chinese hamster ovary cells. Doses in the order of 3000 times that likely to be used in supplementation were required to produce the mutagenic effect of chromium picolinate. Subsequent to this study, the same author had undertaken other studies that appeared to indicate some degree of mutagenicity of chromium picolinate in an *in vitro* system. Based upon these findings, the FSA in the UK are advising consumers not to take supplements that contain chromium picolinate.

Having considered all available information, the OCM considers that the current daily upper limit for Listable complementary medicines of 50µg of chromium, from all dosage forms including CrPic, is adequate to control the safety-in-use of the salt as a nutritional supplement in Listed medicines. However, it was considered this decision should be reviewed if further data suggesting the genotoxic potential of chromium picolinate become available.

CMEC was asked whether, on the present evidence, the use of chromium picolinate in Listed medicines, subject to current dose restriction, is considered appropriate.

Present discussion
A Member commented on the high quality of the evaluation of the toxicity of chromium (III) picolinate, undertaken by TGA's OTC Section.

A Member commented that whilst there is a need to take notice of a substance that causes chromosomal damage and is mutagenic, consideration should also be given to the fact that the concentrations being used to cause these effects are thousands of times higher than the concentrations that occur in human serum. The relevance of these findings are therefore brought into question. It also appears that the mutagenicity is associated more with the picolinate than the chromium. Given that there is a substantial intake of picolinate in the diet, it was considered that there does not appear to be any real cause for concern, particularly when these results were generated on *in vitro* data only, and are yet to be confirmed by an *in vivo* model.

CMEC Recommendation:
Members made the following unanimous recommendation:

Recommendation 41.5

CMEC notes the safety review conducted by the TGA, and recommends that the TGA maintain chromium picolinate for use as an active ingredient in Listed medicines, with a maximum daily dose of chromium of 50μg, as specified in Schedule 4, Part 5, Division 2, Subdivision 2 of the Therapeutic Goods Regulations.

Item 7.4 Safety review of betacarotene as a nutritional supplement.

Background
A TGA Officer introduced this item and explained that, following the publishing of a major review of the safety of a wide range of vitamin and mineral supplements, commissioned by the United Kingdom's food regulator, the Food Safety Authority (FSA), the OCM had identified significant concerns in relation to the use of betacarotene as a nutritional supplement.

Betacarotene is a carotenoid with both antioxidant and pro-oxidant (at high oxygen tension) properties *in vitro*. However there is a paucity of direct evidence that carotenoids are antioxidants *in vivo*. Betacarotene is sometimes referred to as provitamin A as it is converted in the body to Vitamin A (retinol). It is used as a food additive for colour and a source of Vitamin A. It occurs naturally in some fruits and vegetables, thus total intake is from both fruit and vegetables in the diet, from additives in food, and from nutrient supplements.

The synthetic form of betacarotene is all trans (the double bonds are all trans). Many vegetable sources are all trans but conversion to some cis forms occurs during processing. Some algal sources have more cis than vegetable sources. Isomerisation of cis to trans betacarotene occurs during absorption, such that blood levels show virtually no cis isomer present.

Betacarotene is not considered an essential nutrient, and at present there are no dietary intake reference values in Australia, the UK or the USA. However, because betacarotene is a precursor of vitamin A, its dietary intake is typically expressed as part of the recommended dietary intake (RDI) for the latter as retinol equivalents (RE).
The level of betacarotene for use in Listed medicines is not limited, and it is permitted as a food additive without limits on the amount that may be used. In the EU, there is an ADI of 0-5mg/kg/bw, which equates to approximately 350mg/day in a 70kg adult. Betacarotene has GRAS status in the USA for use as a food additive.

During the 1980's, the hypothesis that betacarotene can prevent cancer, particularly lung cancer, was developed from several lines of data. Firstly, observational epidemiological studies, which showed a consistent inverse association between the intake of fruits and vegetables, with further analysis suggesting that betacarotene might be the responsible agent. Secondly, concurrent data from lab and animal studies suggested that betacarotene has antioxidant properties, as it was shown to quench peroxy radicals at low oxygen concentrations.

The accumulating evidence regarding the potential biological benefits associated with betacarotene suggested a positive association must exist between dietary betacarotene and the risk of human cancer. This led to a number of very large intervention trials. Two of these studies – the ATBC (alpha-tocopherol, betacarotene prevention study) and the CARET (betacarotene and retinol efficacy trial) showed an association of betacarotene with increased incidence of lung cancer in smokers and individuals with previous high-level exposure to asbestos. Other studies did not show this increased incidence.

The Expert Group on Vitamins and Minerals (EGVM) in the UK did a risk assessment to estimate a safe upper limit of betacarotene, based on the effects observed in humans at 20mg/day. In the ATBC study the EGVM applied an uncertainty factor of 3 (to get from the lowest observed adverse effect level (LOAEL) to the no observable adverse effect level (NOAEL). An upper level of 7mg/day of betacarotene from supplements was determined. This limit applies to the general population, that is the non-smoker and those not exposed to asbestos, and does not apply to betacarotene in food. However, there is no evidence that betacarotene is unsafe for non-smokers.

In addition, a report in the *Lancet* undertook a meta-analysis of antioxidant vitamins in the prevention of cardiovascular disease. The analysis indicated that the odds ratio for cardiovascular death with betacarotene supplementation was slightly increased (1.1) and also for all-cause death with patients treated with betacarotene (1.07). The odds ratio is the ratio of people with an event to those without the event. An odds ratio of 1 indicates no difference between groups. Where it is less than 1, it indicates the treatment was effective in reducing the risk of that option.

Current discussion
One Member commented that there did not appear to be enough of an increased risk to justify the inclusion of a warning on products containing betacarotene. However, Members were aware that some health professionals had stopped prescribing betacarotene supplements since becoming aware of this study, and they had particular concerns relating to those who may be exposed to passive smoke.

One Member queried the impact of other factors, such as a potential interaction between betacarotene intake and alcohol. Another Member commented that the epidemiological data shows that there is no evidence that betacarotene produces expected therapeutic benefits, and expressed a concern that it might actually be doing harm in some populations. Members discussed whether betacarotene should remain eligible for listing but that some sort of threshold be considered similar to that implemented for nicotinic acid. The question was then raised as to whether or not there was adequate evidence to support this regulatory action.

Members agreed that this was not an urgent public health and safety issue, and suggested a more comprehensive review of all data before a decision is reached.

CMEC Recommendation:
Members made the following recommendation

Recommendation 41.6

CMEC notes the preliminary safety review undertaken by the TGA, and recommends that a full safety review of betacarotene for use as an ingredient in Listed medicines be undertaken.

8. Registration Applications

Members made one recommendation under this item.

9. Variation to a Registered Product

No matters were considered under this agenda item.

10. Matters referred from within the TGA

10.1 Adverse Drug Reaction Advisory Committee reports (ADRAC) - Meeting 268

A Member introduced this agenda item. CMEC noted a number of reviews conducted by ADRAC of adverse reaction reports involving complementary medicines and discussed several case reports. At the request of the Committee, the reports were now itemised according to the report number.

The Committee considered two matters as items 10.2 and 10.3 under this part of the agenda.

Item 10.4 Proposal for label warning regarding chewable tablets

Background
A TGA Officer introduced this item, advising Members that chewable tablets, which often contain palatable formulations, are designed to be chewed rather than swallowed whole. As for other medicines, chewable tablets are required to comply with the Therapeutic Goods Labelling Order No. 69 (TGO 69) which requires medicine labels to contain the name of the dosage form and directions for use, either or both of which will indicate to the user that the tablets are chewable.

Similarly, TGO 56 contains the following interpretation of the chewable tablets: *'chewable' in relation to tablets or capsules, means tablets or capsules which have been formulated to be*

chewed rather than swallowed whole and for which the label includes a direction to chew the tablet or capsule.

Members were advised that in recent months there have been two serious adverse events associated with the use of chewable tablets. There are no recorded reports of choking, oesophageal obstruction or deaths associated with the use of chewable tablets on the ADRU database. However the death of a 5 year-old boy, as a result of inhaling a Combantrin tablet gave rise to a coroner's recommendations which resulted in the Medicines Evaluation Committee (MEC) developing a guideline to cover products that are intended for use in both adults and children (family packs). These guidelines warn of the dangers of labelling medicines such as tablets or capsules for *use in young children* because of the danger of inhalation.

About one quarter of the 418 medicines in "chewable" tablet dosage form listed for supply in Australia, contained the word or words 'child' or 'kid' in the product name. The Australian and international figures on deaths in children attributed to choking are not able to pinpoint the precise involvement of medicines in choking events, but choking hazard warnings are found on some consumer items, including medicines.

Chewable tablets are generally larger than other tablets designed to be swallowed whole and are often presented in novelty shapes such that they may have a greater potential to become lodged in the throat/oesophagus when swallowed whole.

Current legislation requires medicine labels to contain directions for use detailing the method of administration. However, it may be possible for product labelling to comply with this requirement and yet not make it sufficiently clear that a tablet is to be chewed. The TGA sought the opinion of the CMEC as to whether it might be appropriate, given the rare but unfortunate events which can arise, to consider ways in which to assist the medicines industry to fully comply with the intent of labelling requirements to avoid such events.

CMEC was asked to advise regarding appropriate labelling. Members agreed that labelling should highlight the importance of chewing the 'chewable' tablets before swallowing, and in the event of administration to children, ensuring that they do not attempt to swallow, or be forced to swallow, the tablets whole, and to consider crushing the tablets in certain cases.

Present discussion

Members discussed the issue and supported the proposal that the label of products, where the dosage form is a chewable tablet, contain a warning statement emphasising the need to chew the tablet. Consideration was given as to whether a stronger warning, such as "Not to be swallowed" should be directed solely at products aimed at children. However a Member commented that there are similar difficulties with swallowing experienced by the elderly.

Members agreed that as this matter has potentially serious adverse outcomes, particularly with regard to children and the elderly, it would not be inappropriate to require the stronger statement "Not to be swallowed whole" on the label. This statement was seen to encompass the need to warn against the risk of trying to swallow, or forcing children to swallow, the chewable tablet,

and the need to crush the tablets before administering to young children or an individual who has difficulty swallowing.

Members discussed the time frame for enforcing the proposed label warning statements. Keeping in mind that medicines other than complementary medicines are also presented in chewable dosage forms, and the fact that changes to labelling requirements with respect to chewable tablets would need to be consistent across all medicines, Members agreed that modification of Therapeutic Goods Labelling Order No. 69 (TGO69) would be the most appropriate means to give effect to this decision.

CMEC Recommendation:
Members made the following unanimous recommendation:

Recommendation 41.10

CMEC recommends to the TGA that a warning statement should be included on the label of products where the dosage form is a chewable tablet, emphasising the need to chew the tablet, and including the statement "Not to be swallowed whole" or words to that effect.

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 41st meeting:

Item 2 Minutes of CMEC's 40th Meeting

Recommendation 41.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 40, 30 May 2003), are a true and accurate record of that previous meeting.

Item 7.1 Safety Review of Kava (*Piper methysticum*)

Recommendation 41.2

The CMEC endorses the following four recommendations made by the Kava Evaluation Group (KEG), and recommends to the TGA:

Recommendation 1
That:

(i) aqueous dispersions of whole or peeled rhizome of *Piper methysticum*;
(ii) aqueous extracts of whole or peeled rhizome of *Piper methysticum*; and,
(iii) dried whole or peeled rhizome of *Piper methysticum*

are suitable for use as ingredients in Listed medicines for oral use, subject to the following conditions:

(a) the preparation does not contain, for its recommended daily dose, more than 250 mg of kavalactones; and
(b) if the preparation is in a tablet or capsule – the amount of kavalactones does not exceed 125 mg for each tablet or capsule; and
(c) if the preparation is in a tea bag – the amount of dried whole or peeled rhizome does not exceed 3 g for each tea bag; and
(d) if the preparation contains more than 25 mg of kavalactones per dose – the label on the goods includes the following warnings (or words to the same effect):
- Not for prolonged use. If symptoms persist, seek advice from a healthcare practitioner;
- Not recommended for use by pregnant or lactating women; and
- May harm the liver.

Recommendation 2

That *Piper methysticum* may be used in homoeopathic preparations more dilute than a thousand fold dilution of a mother tincture.

Recommendation 3

That:
(i) aqueous dispersions of whole or peeled rhizome of *Piper methysticum*;
(ii) aqueous extracts of whole or peeled rhizome of *Piper methysticum*; and,
(iii) dried whole or peeled rhizome of *Piper methysticum*

are suitable for use as ingredients in Listed medicines for topical application to the rectum, vagina and by spray to the throat.

Recommendation 4

That *Piper methysticum* may be used as an ingredient in Listed medicines for topical application to the skin.

Recommendation 41.3

The CMEC recommends to the TGA that products containing *Piper methysticum* must be Registered prior to their supply, other than:
(i) aqueous dispersions of whole or peeled rhizome of *Piper methysticum*;
(ii) aqueous extracts of whole or peeled rhizome of *Piper methysticum*;
(iii) dried whole or peeled rhizome of *Piper methysticum*;
(iv) products for topical application to the skin; and

(v) homoeopathic preparations more dilute than a thousand fold dilution of a mother tincture.

Item 7.2 Safety review of *Chelidonium majus* (Greater Celandine)

Recommendation 41.4

CMEC notes the safety review conducted by the TGA and recommends that the TGA maintain *Chelidonium majus* as an ingredient for use in Listed medicines, but with a warning statement to be included on the label of oral products. The statement is to advise consumers to use products containing the herb under the supervision of a healthcare practitioner, to caution consumers who have a history of liver disease, and to warn consumers to discontinue use of the herb if particular symptoms indicative of liver problems occur.

Item 7.3 Safety review of chromium (III) picolinate

Recommendation 41.5

CMEC notes the safety review conducted by the TGA and recommends that the TGA maintain chromium picolinate for use as an active ingredient in Listed medicines with a maximum daily dose of chromium of 50µg, as specified in Schedule 4, Part 5, Division 2, Subdivision 2 of the Therapeutic Goods Regulations.

Item 7.4 Safety review of betacarotene

Recommendation 41.6

CMEC notes the preliminary safety review undertaken by the TGA, and recommends that a full safety review of betacarotene for use as an ingredient in Listed medicines be undertaken.

Item 10.4 Proposal for label warning regarding chewable tablets

Recommendation 41.10

CMEC recommends to the TGA that an advisory statement be included on the label of products where the dosage form is a chewable tablet, emphasising the need to chew the tablet, and including the statement “Not to be swallowed whole”.

12. For Information

No matters were considered under this agenda item.

13. Other business

No matters were considered under this agenda item.

The Chair closed the meeting at 4.31