TGA THERAPEUTIC GOODS ADMINISTRATION

Commonwealth Department of Health and Ageing

CMEC 37

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Thirty Seventh Meeting
30 August 2002

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
ANZFA	Australia New Zealand Food Authority
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
GRB	Geographical Risk of BSE
JHTF	Joint TGA/Industry Herbal Task Force
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 thirty seventh meeting of the Complementary Medicines Evaluation Committee was held at the at the Therapeutic Goods Administration, Canberra, in Conference Room 1 from 9.30 am to 2.30 pm on Friday 30 August 2002

Members of CMEC present were:

Professor Tony Smith (Chair)

Mr Kevin Ryan
Dr Heather Yeatman
Dr Vicki Kotsirilos
Dr Iggy Soosay
Associate Professor Douglas Moore
Ms Val Johanson
Associate Professor Bill Webster

Expert Advisers to the Committee present were:

Associate Professor Alan Bensoussan
Dr Tim Carr
Mr Philip Daffy
Mr John Lumby
Mr Robert Medhurst
Ms Robyn Minski
Dr Derek Weir

Present from the TGA, at various times during the meeting, were:

Mr Pio Cesarin
Dr Fiona Cumming
Dr John Hall
Dr David Briggs
Dr John McEwen
Dr Jennifer Elijah
Dr Bogdan Sikorski
Mr Rob Keane
Ms Michelle McLaughlin

1. Procedural Matters

1.1 Opening of Meeting

The Chairman opened the meeting at 9.30 am and welcomed CMEC Members, Expert Advisers and TGA staff and gave an opportunity for those present to introduce themselves.

1.2 Apologies

Members noted that Dr John Ryan, Professor Stephen Myers and Professor Gillian Shenfield were unable to attend the meeting.

1.3 Conflict of Interest

Members submitted conflict of interest declarations specific to agenda items for this meeting. The Chairman briefed the Members about general conflict of interest issues, which apply to TGA committees and about the annual and meeting by meeting requirements.

2. Confirmation of Minutes of CMEC 36 (26 July 2002)

The minutes of the thirty-sixth meeting of CMEC were accepted as an accurate record of proceedings, with minor amendments.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 37.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 36, 26 July 2002), as amended, are a true and accurate record of that previous meeting.

3. Guidelines on levels and kinds of evidence to support claims for therapeutic goods (Guidelines)

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

5.2 Folic Acid Dissolution Requirement

Introduction
Advice was requested from Members on a proposal from industry for implementing dissolution requirements for certain folic acid preparations recommended by Members at CMEC 30. In particular, Members were asked to consider if the industry proposal was consistent with the public health and safety concerns originally identified by the Committee (CMEC 30, October 2001).

Background
The Office took carriage of this issue in October 2001 following the earlier identification by the Medicines Evaluation Committee of potential problems with folic acid preparations in Australia following concerns raised in the USA in relation to the release and bioavailability of folic acid in various products. A study by Hoag *et al.* (1997), conducted by the University of Maryland at Baltimore, found that six of nine products failed dissolution tests. The failure of such products to meet dissolution standards and the implication this might have for reduced

bioavailability was a matter of concern, given that folic acid supplements taken by women before and during early pregnancy are indicated for the reduction in risk of foetal NTD.

The *British Pharmacopoeia* (BP) monograph Folic Acid Tablets does not include a dissolution requirement. However, the *United States Pharmacopoeia* 24th Edition (USP24) monograph for Folic Acid Tablets and the general monograph on Nutritional Supplements do include dissolution tests for folic acid. Currently, there is no requirement in TGO No.56 *General standard for tablets, pills and capsules* for dissolution testing of folic acid tablets or tablets containing folic acid. The current legal requirement for folic acid tablets or tablets containing folic acid is compliance with the TGO No. 56 test for disintegration.

Dissolution testing was performed by the TGA laboratories on 51 folic acid tablets available in Australia which were claimed to contain 100 micrograms or more of folic acid per dosage unit. The products selected for analysis represented a range of sponsors/manufacturers, various concentrations of folic acid (100 microgram or more per dosage unit) and products where folic acid was not the sole ingredient. Only tablets were included in the survey. Five of the products contained only folic acid as an active ingredient at greater than 500 micrograms. The remaining 46 products contained between 100 and 500 micrograms folic acid and contained more than one active ingredient.

At CMEC 30 (October 2001), the Committee recommended to the TGA that a dissolution standard be mandatory for folic acid preparations, in tablet form, of a strength of 100 micrograms or more per dosage unit. (Recommendation 30.11).

The recommendation was made following consideration of TGA testing results that found that 10 out of 51 samples of folic acid supplements failed to comply with the dissolution requirements in the USP24. While compliance with the USP24 dissolution requirements was not mandatory, the issue was considered to be of major concern as absorption of orally administered medicines in solid forms such as tablets is largely dependent on the active components being in the dissolved state.

Sponsors were formally notified in May 2002 about the additional requirement for folic acid preparations in tablet form, of a strength of 100 micrograms or more per dosage unit. The conditions were to come into effect on 25 November 2002.

An industry association was concerned about the ability of the complementary medicines industry to meet the additional conditions of listing/registration for folic acid supplement preparation, in tablet form.

At CMEC 36 (July 2002), the Committee recommended to the TGA that:

- all folic acid tablets including an indication or a claim related to neural tube defects (NTD) on the ARTG;
- all folic acid tablets likely to be taken by women (including those likely to be taken by both men and women) and containing 400 micrograms or more of folic acid; and
- all folic acid only formulations containing 400 micrograms or more of folic acid,

should comply with the proposed dissolution requirements, by 25 November 2002, and that a letter be sent to health professionals and information be posted on the TGA website advising that these products are to comply with the above requirements.

CMEC also advised the TGA that it would defer making a decision on the dissolution requirements for:

- any remaining folic acid tablets containing 400 micrograms or more of folic acid; and
- all folic acid tablets containing less than 400 microgram folic acid (Recommendation 36.6).

The present discussion was aimed at addressing these last two dot points.

Present discussion
A Member queried the type of folic acid preparations available in Australia. The Committee was advised that folic acid could be part of a multivitamin preparation indicated specifically for a target population or it could be included as a sole active ingredient in a preparation.

As noted previously, the current legal requirement for folate supplements in Australia is compliance with the TGO No.56 test for disintegration. However, in the case of folic acid supplements, the principal mode of absorption occurs in the proximal jejunum and when taken without food, the gastric retention time and the time to pass through to the jejunum can be very short. This means that the folic acid in products with inadequate dissolution characteristics, are theoretically less bioavailable. Given the short absorption window for folic acid, a requirement to comply with a dissolution standard may be particularly important.

Members expressed concern that those folic acid products marketed in Australia, which had failed the dissolution requirement and therefore had a lower potential for absorption in to the body, might not be able to be as confidently prescribed by professionals to their patients.

The Committee was reminded that it needed to provide clear advice to the TGA as to which folic acid tablets should comply with the proposed dissolution requirements and by when. In doing so, it was recognised that a reasonable time for compliance should be recommended to taking into account both the public health implications and the commercial realities of reformulation.

The Committee considered it imperative that those formulations relied upon by the most at-risk populations were those taking folic acid at or above the recommended 400 micrograms per day. Members therefore considered that these products, regardless of the proposed target group or indication, should comply with the proposed dissolution requirements by the previously foreshadowed date of 25 November 2002. This amends and simplifies the recommendation previously made to the TGA (Recommendation 36.6) where the compliance conditions were dependent on the indication or target group.

Members considered that other folic acid-containing preparations, below 400 micrograms per day, should also be required to comply with the proposed dissolution requirements because they may also be relied upon for important public health and safety outcomes. For simplicity however, it was decided to focus on those products between 100 and 400 micrograms per day and to require compliance for these products by 25 November 2003, or by a date to be negotiated with the industry.

CMEC Recommendation
The CMEC resolved to recommend that:

Recommendation 37.3

CMEC recommends to the TGA that:

- **All tablets containing 400 micrograms or more of folic acid should comply with the proposed dissolution requirements by 25 November 2002 and publicity be directed to health professionals and information be posted on the TGA website advising that products containing 400 micrograms or more of folic acid must comply with these requirements; and**
- **All folic acid tablets containing between 100 and 400 micrograms of folic acid must comply with the proposed dissolution requirement, by 25 November 2003, or by a date to be negotiated with the industry.**

Members also considered two other matters under agenda item 5.

6. Evaluation of New Substances

6.1 Magnesium phosphate dibasic trihydrate (MPDT)

Introduction
The OCM sought advice from the CMEC as to whether or not magnesium phosphate dibasic trihydrate (MPDT) was suitable for use as an ingredient in listable therapeutic goods, and if so, whether there should be any restrictions imposed on its use. The Committee was asked to consider this safety evaluation of MPDT with a view to switching the regulatory status of MPDT from registrable to listable substance.

Summary of evaluation report
A TGA Officer introduced this item advising Members that the OCM had received an application from a sponsor, for approval of including MPDT as an ingredient in listable therapeutic goods.

MPDT occurs in nature as the minerals newberyite and phosphor-roesslerite. It is a white crystalline powder, which is slightly soluble in water and soluble in diluted acids. MPDT is a well characterised substance and its chemical properties are well understood - it is described in the *Food Chemical Codex IV* as an nutrient, dietary supplement, leavening agent and pH control agent. When approved for listing, specifications for MPDT must comply with the monograph in the *Food Chemical Codex IV*, (1996).

In terms of therapeutic use, MPDT has a relatively long history of use as a cathartic/purgative agent, but a relatively short history of use as a mineral supplement. MPDT is unlikely to be used as an excipient.

MPDT, as such, is unlikely to occur in food, but is ionic components, Mg and phosphate, or phosphorus, are found in food in reasonably large quantities. These ions are considered essential nutrients for human beings with food providing the greatest level of exposure.

At present, MPDT is an active ingredient in 14 listed products and 2 registered products. Of the 14 entries for listed products, 12 entries are for homoeopathic goods. The ARTG has no entries for products containing MPDT as an excipient.

An average daily dietary intake of Mg for adults in Australia is in the range of 200 to 500 mg, with male intake being about 20% higher. An average dietary intake of phosphate has not been determined, but that of phosphorous is in the range of 1000 to 2500 mg, with male intake being about 30% higher than female intake. The Australian Recommended Dietary Intake (RDI) for Mg for healthy adults is 320 mg/day for males and 270 mg/day for females. The RDI for phosphorus (no RDI for phosphate) is 1000 mg/day for healthy adults of either gender.

In Australia, EU and US, MPDT is widely used in food industry as a leavening agent and pH control agent, and for that uses it has a generally recognised as safe (GRAS) status in the US. At present, the use of MPDT as mineral supplement appears to be limited to the sponsor's products. There is no recommended daily maximum intake for Mg, but the maximum tolerable daily intake from all dietary sources for phosphorus has been set by Joint FAO/WHO Expert Committee on Food Additives (JECFA) at 70 mg/kg/day.

Metabolically, MPDT behaves as a source of magnesium cation and a bivalent hydrogen phosphate anion. Both ionic components of the salt play an important role in the electrolyte balance of the body. Also, both magnesium and phosphorous are essential components of many enzyme systems involved in the production of energy and synthesis of many cell matrix components, and both are utilised in some tissues as building materials (e.g., bones). Absorption of both ions, which occurs in intestines, is limited and inversely dose-dependent, with higher doses resulting in lower absorption. Once absorbed, excess amounts of both Mg^{2+} and HPO_4^{2-} ions are rapidly excreted in urine, but faeces is the major route of excretion for phosphate ions. Increased or reduced availability of either magnesium or phosphate in the organism, beyond control of homeostatic mechanisms, can produce changes in volume and/or osmolality of plasma and interstitial fluid, and aberrations in various metabolic systems in the body. In more extreme circumstances, for instance when renal function is impaired, hypermagnesaemia and hyperphosphataemia may develop, which may be life threatening.

Due to the lack of the salt-specific data, toxicity of MPDT could only be assessed in terms of toxicity of its ionic components. Animal data indicate that both acute and chronic oral toxicity of magnesium and phosphate is relatively low. In some short-term studies, particularly in rodents, high doses of monophosphates produced calcification of soft tissues including nephrocalcinosis, but such changes were not observed in further studies, suggesting that other dietary factors may influence the calcification response. Studies with various magnesium salts provided no evidence of genotoxicity, carcinogenicity and reproductive toxicity. Various phosphate salts were also devoid of mutagenic activity, and produced no maternal toxicity or teratogenic effects in rodents and rabbits. Reproductive function was not affected in rats fed diets supplemented with phosphoric acid. However, the toxicity data package reviewed for this application was not comprehensive as indicated, for example, by the lack of long-term exposure and carcinogenicity investigations for phosphate salts, or phosphorus.

Clinical data on supplementation at relatively high doses with various magnesium salts and with phosphorous suggested that both short- and long-term supplementation was not detrimental to health in healthy individuals. Because MPDT is virtually insoluble in water,

excessive oral intake of the salt is unlikely to result in serious toxicity. Nonetheless, taken at doses above about 3g, MPDT will induce diarrhoea, but a minimal dose required to produce this effect has not been established. Extremely high and/or repeated doses of magnesium salts (Magnesium sulphate), but not MPDT, have been reported to produce toxicity symptoms consisting of metabolic alkalosis, hypokalaemia and cardiorespiratory changes.

There are no adverse reaction reports for MPDT as such, but 4 reactions were reported to ADRU for one product, a multi-ingredient formulation. The reaction, which was most likely caused by the product, was "dizziness". In addition, the WHO adverse reactions database contains reports of two adverse events for the same product. One is for jaundice/haemolytic anaemia and another for diarrhoea. None of the reactions caused or associated with a multi-ingredient preparation can be positively attributed to one of its ingredients.

Present discussion:
It was noted that out of the 14 listed products on the ARTG, 12 of these were homoeopathic preparations. These homoeopathic preparations may be containing 1,000-fold dilution, or a lesser dilution, of that mother tincture.

At present, the only magnesium phosphate salt permitted ('grandfathered') for use in Listed therapeutic goods is 'magnesium phosphate', which is defined as 'magnesium phosphate tribasic pentahydrate' [$Mg_3(PO_4)_2$].

Members considered that there were no significant safety issues as both ionic components of MPDT play an important role in the maintenance of osmolality of plasma and interstitial fluid, and in the functioning of many essential enzymatic systems in the body. In addition both ions are principle components of bone.

A Member was concerned about this substance being given to patients with renal impairment and children and suggested that a warning label be included if this product was approved for listing. The Committee was advised that because of relatively poor intestinal absorption of the salt and a relatively rapid urinary elimination of both ionic components of the salt, systemic toxicity was unlikely. In addition, no evidence of systemic toxicity was obtained after relatively high oral doses of either of the ionic components of the salt in animals or humans. The Committee agreed that there would not be a need for a warning statement and agreed to approve MPDT for use as an ingredient in listable therapeutic medicines.

CMEC Recommendation
The CMEC resolved to recommend that:

Recommendation 37.4

CMEC recommends to the TGA that magnesium phosphate dibasic trihydrate is suitable for use as an ingredient in listable therapeutic medicines.

7. Safety or Efficacy Reviews

No matters were considered under this agenda item.

8. Registration Applications

One recommendation was made 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 ADRAC Report

Members were provided with a brief overview of the role and function of the Adverse Drug Reactions Unit (ADRU).

Members noted the Report from the 262nd meeting of the Adverse Drug Reaction Advisory Committee (ADRAC) and discussed several reports.

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 37th meeting:

Item 2 Minutes of CMEC's 36th Meeting

Recommendation 37.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 36, 26 July 2002), as amended, are a true and accurate record of that previous meeting.

Item 5 Action Arising from Previous Meetings

Item 5.2 Folic Acid Dissolution Requirement

Recommendation 37.3

CMEC recommends to the TGA that:

- All tablets containing 400 micrograms or more of folic acid should comply with the proposed dissolution requirements by 25 November 2002 and publicity be directed to health professionals and information be posted on the TGA website advising that products containing 400 micrograms or more of folic acid must comply with these requirements; and
- All folic acid tablets containing between 100 and 400 micrograms of folic acid must comply with the proposed dissolution requirement, by 25 November 2003, or by a date to be negotiated with the industry.

Item 6 Evaluation of New Substance

Item 6.1 Magnesium phosphate dibasic trihydrate

Recommendation 37.4

CMEC recommends to the TGA that magnesium phosphate dibasic trihydrate is suitable for use as an ingredient in listable therapeutic medicines.

12. For Information

No matters were considered under this agenda item.

13. Other business

The Committee considered one matter under this agenda item.

The meeting closed at 2.30 pm on Friday 30 August 2002. The next meeting is scheduled to be held on Friday 18 October 2002.