Australian Government

Department of Health

Therapeutic Goods Administration

ACCM 14th Advisory Committee on Complementary Medicines

Ratified Minutes

2nd August 2013

TGA Health Safety Regulation

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADR	Adverse Drug Reactions
ANZTPA	Australia New Zealand Therapeutic Products Agency
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
BP	British Pharmacopoeia
CG	Compositional Guideline
CMEC	Complementary Medicines Evaluation Committee
CSU	Committee Support Unit
EFSA	European Food Safety Authority
EU	European Union
FSANZ	Food Standard Authority Australia and New Zealand
GRAS	Generally Recognized as Safe
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
MAG	Marketing Authorisation Group
NOAEL	No Observable Adverse Effect Level
OCM	Office of Complementary Medicines
OPR	Office of Product Review
RNA	Ribonucleic acid
TGA	Therapeutic Goods Administration
USP-NF	United States Pharmacopeia and National Formulary

The Advisory Committee on Complementary Medicines (ACCM) held its fourteenth meeting at the Therapeutic Goods Administration from 9:30 am to 4:00 pm on 2 August 2013.

Members of ACCM present

Professor Alan Bensoussan (ACCM Chair)

[redacted]

Present from the Therapeutic Goods Administration

Ms Jenny Burnett (ACCM Secretary)
Ms Trisha Garrett (Head, OCM)
Ms Philippa Horner (Principal Legal Adviser) (present for part of the meeting)
Professor John Skerritt (National Manager) (present for part of the meeting)
Dr Angeliza Querubin (OCM)

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9:30am, welcoming ACCM members, particularly those attending their first meeting, and TGA staff including the National Manager. [redacted]

[redacted]

[redacted]

1.3 Meeting declaration of interest

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

Action 14.1

Members requested that the guidance documents for TGA statutory committees related to conflict of interest issues be uploaded onto Govdex.

Outcome 14.1

The TGA advisory committee guidelines on managing conflicts of interest are available both on the TGA website and on Govdex.

2. Minutes of previous meetings

2.1 Ratification of ACCM 13th minutes

Outcome 14.2

ACCM confirms that the draft minutes of its previous meeting, ACCM 13, are a true and accurate record of that meeting.

3. Actions arising from previous meetings

3.1 Food/medicine interface issues

A TGA officer gave a presentation outlining the regulatory frameworks that apply to food and medicines in Australia. The reasons why differentiation between these types of goods was important both to industry and regulators were emphasised.

The committee members discussed the issue of differentiating between food and medicines, particularly in relation to the regulation of complementary medicines. Examples of where foods could be considered a medicine, if used in a way that modifies a physiological process in the body, were provided by members. The issue that certain foods are now marketed with health claims, and also the possibility that goods have been presented as foods in an attempt to remove them from regulatory requirements of the *Therapeutic Goods Act 1989*, was raised.

A member asked whether foods that are presented as supplements would be regulated by the TGA or FSANZ. The TGA officer explained that where the goods are subject to a food standard, then they will be regulated by FSANZ. The discussion led to whether the addition of certain medicinal ingredients to a food will result in it being considered therapeutic goods or whether it would remain a food. It was confirmed for members that in these cases, despite containing active ingredients, the goods would still be considered food, albeit a non-compliant food.

The on-going need for clarity in differentiating goods on the food/medicine interface, and the relevance for ACCM consideration of complementary medicine issues, was noted by the committee.

Action 14.2

Members requested that the food and medicine interface presentation be uploaded on Govdex.

Outcome 14.3

The food and medicine interface presentation has been uploaded on Govdex.

3.2 New registered complementary medicine – [redacted]

[redacted]

4. Evaluation of New Substances

4.1 Substance: Cognizin Citicoline

Background

A TGA officer introduced this item, advising members that an application has been received for evaluation of citicoline (Synonyms: Cognizin®, CDP-choline, choline cytidine 5'-pyrophosphate, cytidine 5'-diphosphocholine) for use as an active ingredient in oral listed medicines. Citicoline is intended as a source of choline supplementation at doses of 250-500 mg/day.

Citicoline is an endogenous compound in mammals, being an essential intermediate in the synthesis of phosphatidylcholine. Following ingestion, citicoline is hydrolysed in the gut to cytidine and choline, with evidence for the rapid deamination of cytidine to uridine in humans. At a dose of 500 mg/day, citicoline will provide about 107 mg choline and 250 mg cytidine/day.

In the US, Cognizin® citicoline has self-affirmed Generally Regarded as Safe (GRAS) status for use in food (2009). The applicant stated that Cognizin® citicoline is a component of supplement products at daily doses of up to 10 g. However, based on the intended uses and at the intended use levels (details not provided other than the inclusion of citicoline in food at up to 250 mg/serving), the estimated maximum daily intake of citicoline from food at the 90th percentile for the total population was 2000 mg/day. The applicant reported that since 1994, 15 metric tonnes of Cognizin® citicoline have been sold in the US.

Neither cytidine nor uridine is available for use in listed medicines. Cytidine is present in the diet in the form of RNA but from the information in the application, the typical dietary intake of cytidine is unclear. Given that the preclinical and clinical safety data have a number of shortcomings, to strengthen the application, the applicant was asked to provide an estimate of the likely level of dietary intake of cytidine in a typical Western diet and comment on how this compares with the intake of cytidine at the proposed maximum daily dose of citicoline when used in listed medicines. However, the applicant did not provide any relevant data referring to these issues.

The TGA identified a number of gaps in the pre-clinical and clinical safety data submitted by the applicant. The duration of some toxicity studies with citicoline was no more than three months and no developmental/reproductive toxicology studies were included. The applicant was asked to comment on the absence of this data and the implications for establishing the safety of citicoline for use in listed medicines. The applicant justified the lack of developmental or reproductive safety data by the fact that there were no adverse effects on male and female reproductive organs reported in repeat dose oral toxicity studies conducted in rats and dogs. The applicant noted that the reproductive organs did not show treatment-related abnormalities and that the doses used were approximately 180-fold greater than the intended intake level of Cognizin® citicoline at 500 mg/day. However, as these studies were not designed to investigate foetal effects, these justifications did not provide assurance for the safety of citicoline in pregnant or lactating women.

Four clinical trials with citicoline were conducted in healthy volunteers and in three of these trials, no adverse events were reported. The other clinical trials with citicoline (500-4000 mg/day) were studied in patient populations with serious conditions including stroke, bipolar disorder and cocaine or methamphethamine dependence. However, there was a degree of uncertainty in extrapolating data from these studies given that the patients already have a serious condition and any adverse outcomes cannot be conclusively linked with citicoline. Except for a recently published 9-month multi-centre open label trial in patients with mild cognitive impairment, other trials were of 5 days to 3 months duration only.

The TGA noted that an application by Kyowa Hakko Europe Gmbh was made to the Food Safety Authority of Ireland in March 2012 which gave a favourable opinion. However, questions were raised by several EU member states and citicoline is currently being reviewed by EFSA (European Food Safety Authority). The EFSA report was expected to be released on August 2013.

In the absence of data to determine dietary exposure to cytidine; the limited preclinical data; the lack of evidence for safety of use in all patient populations, ACCM was asked to advise on whether the submitted safety data package was sufficient to establish the safety of citicoline for use in oral listed medicines.

Discussion

The members discussed the availability of data on the reproductive safety of uridine and cytidine, noting that there was insufficient data to support safety of citicoline with respect to a developing foetus. Whilst the intake of RNA as food was recognised, the matrix effect associated with this type of intake was considered to negatively impact on its relevance in establishing the safety of citicoline use as a medicine. One member raised the possibility of pregnant women being a target population for listed medicines containing citicoline and that, given this and the lack of specific safety data, use in pregnancy advisory statements may be appropriate. However, there was a consensus amongst members that this may not suffice and there was in fact insufficient evidence to support safe use of the substance in pregnant or lactating women.

The members discussed the preclinical toxicology studies using citicoline and the findings of mineral deposits in rat kidneys following administration of citicoline at 1500 mg/kg/day for 90 days. The members commented that the observed mineral deposits found may have been related to the dosage of citicoline used or other chemical properties of the product.

During review of the submitted clinical trial data, members noted the reporting of adverse events and commented on the likelihood that these were associated with the pre-existing medical conditions of the patient populations used in the trials. It was concluded that this possibility reduced the value of the trials in establishing the safety of citicoline when used in the general population. It was noted that the Cochrane review showed that citicoline was generally well tolerated. It was felt that the use of 'high risk' patients in trials should create the potential for a greater chance of adverse events, however none had been reported. One member raised concerns on the effects of citicoline on the cardiovascular system and the lack of data on liver and kidney function in the clinical trials.

Since Cognizin® Citicoline has a self-affirmed Generally Regarded as Safe (self-affirmed GRAS) status for use in food, the members asked for more information on the meaning of GRAS. A TGA officer explained that products with a self-affirmed GRAS status have been reviewed by 'an independent panel of experts' to review safety concerns, but not by the US Food and Drug Administration (FDA).

The committee discussed the possibility of regulatory conditions being imposed on the use of citicoline in listed medicines, given that, once approved, permitted ingredients can be used in any listed medicine.

Given that the clinical trials included studies of efficacy of citicoline in patients with various medical conditions, a question was raised by a member about the possibility that it may be used for the treatment of serious conditions such as Alzheimer's disease. A TGA officer provided an assurance that, while the applicant did not identify any therapeutic indications for the use of citicoline in the application, the Australian regulatory framework does not allow high level indications to be made for listed medicines.

The committee acknowledged the extensive clinical data and wide usage of citicoline, particularly in food, and the indication that it is generally well tolerated in humans. However, there was a concern with the number of deaths in one clinical trial which required further investigation and that, despite its apparent wide usage, there was a lack of ADR reporting to support its wide usage. Members noted the delay in publication of the EFSA report and the possibility that safety concerns identified in the TGA evaluation, particularly those associated with use in pregnancy, might be addressed in that report.

Advice 14.1

ACCM advises TGA that the submitted safety data package is not sufficient to establish safe use of citicoline in listed oral medicines. The committee acknowledges the extensive use of

the substance in other jurisdictions, and the safety of choline but, in the absence of detailed use and adverse effect data and the outcome of the EFSA considerations, appropriate safety has not been established at this time.

4.2 Substance: Glutathione

Background

A TGA officer introduced this item, advising members that an application has been received for evaluation of glutathione (GSH) (trade name Setria®) for use as an active ingredient in oral listed medicines. GSH is generally known as an endogenously produced antioxidant and, although not specifically proposed by the applicant, its use as an active ingredient in oral complementary medicines is likely to be in such a role. The applicant has indicated that GSH would be for oral use, at a prolonged duration, in products providing doses of 250 to 1000 mg/day, in either capsule or powder forms.

Apart from its ubiquitous presence in the human body, GSH is present as an endogenous component in various food products. The dietary intake of GSH is widely variable, but it has been estimated that typical dietary intake in the USA from endogenous GSH in food is up to 150 mg/day.

GSH is currently available in the USA as a dietary supplement (with recommended doses ranging from 50 to 1500 mg/day), having gained in 2009 self-affirmed GRAS status, without formal assessment by the FDA. However, the GRAS application was reviewed by a panel of expert independent scientists who provided a consensus statement recommending that GSH was safe for use, "under the conditions of intended use, as a food ingredient". Based on that approval, GSH has been added to a variety of food products marketed in the US including meats, milk, cheese and many others, with a serving dosage between 10 and 300 mg.

A number of GSH containing products have been used in the USA as orphan drugs for the treatment of AIDS-associated cachexia and other serious disorders such as Parkinson's disease and diabetes.

In Canada, GSH is "classified as a Natural Health Product (NHP) under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations", and so is available for use as an ingredient in natural health products. Currently there is no monograph for this substance published on Health Canada website; thus Health Canada evaluates the quality, safety and efficacy of individual products containing glutathione as an active ingredient prior to licensing.

Currently, GSH is permitted for use in listed medicines as an excipient ingredient without any restrictions. In July 2013, there were four listed sunscreen products on the ARTG containing GSH at 4 mg/g, and one listed oral medicine containing an unknown amount of GSH.

GSH has previously been assessed and approved by the TGA for use as an excipient in oral listed medicines. The evaluation at that time considered the proposed use of GSH as an exogenous antioxidant source in probiotic products. The assessment of GSH safety in this context did not focus on potential large bolus doses and, in particular, subsequent possible effects on the gut. The current TGA assessment of the application's safety dossier has identified limitations in the data used to support the safety of GSH at the proposed dose and route of administration in humans.

One of the safety issues identified by the TGA relates to a recently published human clinical study, which reported lightening of skin colour following oral intake of GSH twice

daily at 250 mg for four weeks (Arjinpathana & Asawanonda, 2012). While this study was submitted in the application dossier, the applicant did not discuss the safety implications associated with this outcome.

There were studies that suggest GSH and/or the products resulting from its enzymatic breakdown have genotoxic effects. Since it is unclear to what extent high, repeat oral doses of GSH increase GSH levels in the body, the genotoxic risk presented by high supplemental doses of GSH is also uncertain. Although it is unlikely that oral intake would result in prolonged increased levels of GSH in the body, it is possible that both the liver and kidneys may be exposed to transiently increased GSH levels after repeat high oral doses. More likely, the enzymatic breakdown of relatively high oral doses of GSH in the intestine may potentially result in relatively high local exposure to genotoxic factors. These potential risks have not been addressed by the applicant.

The potential of GSH to be carcinogenic in humans was not addressed adequately by the applicant because of a lack of specific carcinogenicity data. Instead, a number of studies were provided which investigated the effects of GSH on experimentally-induced carcinogenesis. The TGA noted that none of these studies were designed to investigate the potential of GSH as a carcinogen, nor was the safety of GSH investigated using appropriate study parameters. All of the studies included combined treatment regimens with GSH and other compounds. These data were considered irrelevant to the assessment of the carcinogenic potential of GSH. The TGA noted that the application relied largely on the endogenous nature of the substance to support its safety.

The TGA's opinion is that, as discussed above in relation to genotoxicity concerns, risks in relation to carcinogenicity are likely to be highest in the gut.

Another safety concern was the potential for oral GSH intake to affect reproduction and foetal development. The TGA noted that the reproductive and developmental toxicity studies conducted with GSH in animal models (mice and rabbits) were limited in scope. Foremost, the studies were not adequately designed to investigate foetal effects, dosing did not encompass pre-mating and mating periods and the route of administration of GSH was intravenous. However, as discussed above, the possibility that oral GSH results in significantly increased levels of GSH in the body is unlikely and hence the likelihood that GSH may have an effect on reproduction and development is low.

The chemical nature of GSH suggests that high oral doses may theoretically interact with different medicines within the gastrointestinal tract. The applicant did not provide any information on potential interaction between GSH and other medicines taken concomitantly. It is known that intravenous doses of GSH can interact with certain medicines and their metabolites, although this is not considered relevant to oral dosing with GSH (prolonged elevated circulating levels of GSH are not achieved by oral dosing).

Two clinical trials which assessed the general safety of oral GSH (up to 1000 mg/day) in healthy adults had short treatment periods (4 weeks). Therefore, the studies alone were not considered sufficient to establish the safe prolonged oral use of GSH up to the proposed dose of 1000 mg/day. The studies reported a small number of minor adverse events associated with GSH intake. They were mainly gastrointestinal complaints including flatulence, loose stools or indigestion.

In 2011 the TGA evaluated and permitted the use of GSH as an excipient ingredient in listed medicines. The evaluation performed at that time identified a number of issues in the safety data. However, given the substance's ubiquitous nature and the context of its proposed use, the balance of evidence was considered acceptable.

More recently, the TGA has evaluated GSH for use as an active ingredient. When considering prolonged high level exposure and potential bolus dosing that may arise when used in this context, the previously identified concerns must be re-assessed. In addition to

this, the new report of GSH causing significant skin lightening in humans, which may lead to increased risk of skin damage from UV radiation, must be taken into account to determine the suitability of GSH as an active ingredient in oral listed medicines. ACCM was asked to advise whether, in association with an application currently before the TGA, the balance of evidence supports the safe use of glutathione in oral listed medicines.

Discussion

A member provided a brief description of GSH metabolic pathway involving some of its conjugates (eg. hydroquinone - a common ingredient in cosmetic products) which are known to be toxic. The concern was that at a high concentration, these may pose genotoxic and carcinogenic risk. It was suggested that placing a limit on the dosage of GSH may prevent the accumulation of such toxic metabolites. However, in the normal population the proposed GSH dosage appears relatively safe; patients who would be at increased risk may include those taking concomitant medicines.

Another concern raised by members was the potential for concomitant use of glutathione precursors (such as N-acetylcysteine and s-adenosyl methionine) to contribute to the exposure to toxic metabolites. This risk was compared to that already posed by concomitant use of ingredients currently permitted for unrestricted use in listed medicines. A suggestion was made to add a precautionary statement about the potential for interactions with other medicines. However, this raised the question of whether it was appropriate to add this warning without strong evidence to support it. It was noted that the clinical relevance of the combination of these agents in humans is not well known.

The members noted that GSH is present in foods and in normal human metabolism, which provides a context of safe use. However, since there is the possibility that GSH, as an active ingredient in listed medicines, may be used at a bolus high dosage, the safety of GSH in this context may not be analogous to the safety profile observed from food consumption. The absence of genotoxicity data was also of concern, although it was noted that in most instances where a substance is shown to be genotoxic at high doses, this may not correlate with carcinogenicity at usual therapeutic doses. In this case, the greatest concern was the multiplicity of confounders and the likelihood that the target patient population maybe exposed to the same type of ingredients via concomitant use of medicines with similar proposed therapeutic effect. It was postulated that a dose limit would be required to limit this risk.

The safety of GSH in patients with serious conditions was discussed. A member pointed out a study which reported no side effects in patients with cystic fibrosis after GSH consumption. The members noted that there are gaps in the pre-clinical and clinical studies to support the safety of GSH.

Members reviewed the clinical trial investigating GSH intake and skin lightening. The study reported the skin lightening effect after oral intake of GSH (up to 500 mg/day) and it was considered to be of merit. It was noted that the skin lightening effect may occur at GSH exposure levels that are greater than the normal daily intake obtained from the diet. The members discussed the possibility of a strong market demand for products that have a skin lightening effect and the presence of these products in countries such as Australia where the risks associated with melanoma are high. A suggestion was made to include an advisory statement for medicines containing GSH – members noted particularly that the wording of such statements was important and should not identify 'skin whitening' nor 'photosensitivity'. An upper dosage limit of 500 mg was also proposed by the members as appropriate for its use in listed products.

Advice 14.2

ACCM advises the TGA that given the context of wide use and its endogenous nature, glutathione is generally considered safe for use in oral listed medicines. However, the committee had concerns regarding potential confounding effects with other agents and its effect on melanin production which should be mitigated by a suitable advisory statement and a daily dose limit of 500 mg.

5. Evaluation of new Registered Complementary Medicines

Nil

6. Regulatory issues and updates

6.1 Regulatory Updates - Current TGA Consultations

A TGA officer provided a number of updates on current TGA consultations and reforms.

An update on complementary medicine reforms noted that this work includes some proposed changes to the *Therapeutic Goods Act 1989* (the Act). It was clarified that the decision to proceed with most of the reforms, and any changes to the Act, rests with the government and not with the TGA. An exception is reform arising from the Auditor General's report that can be implemented within the existing regulatory framework – this is within the TGA's remit.

Other activities relate to the TGA external education/communication framework that was put in place in late 2012. The framework aims to improve understanding of the role and responsibilities of the TGA, improve transparency, enhance engagement with external stakeholders, and develop better mechanisms for two-way communication with consumers, health professionals and industry. According to a survey, many people have little understanding of certain terms, such as 'efficacy' and 'risk', or the difference between listed and registered medicines. Mention was made of the labelling and packaging review, which potentially will affect prescription medicines more than complementary medicines, and changes to compounding regulations, which is particularly relevant to medicines administered intravenously.

A brief summary of activities associated with the commencement of the new Australian New Zealand Therapeutic Products Agency (ANZTPA) in 2016 was provided to members. Work relating to harmonising regulatory approaches and business processes is on-going, noting that the New Zealand government is still in the process of determining the scope of its proposed framework for regulating natural health products. Members discussed the roles of the existing TGA statutory advisory committees in the new ANZTPA framework and the fact that these were still being developed.

Issues identified in the current advertising reform program were discussed with members. These included recognition of the need for a faster and simpler review process; the current limitations on advertising of scheduled and unscheduled over-the-counter medicines and how this is undertaken with regard to both the scheduling and the advertising frameworks; possible extension of advertising regulations to include the internet and pay TV; and advertising to practitioners.

Members also briefly discussed potential changes to the regulation of advertising to practitioners and the current recognition of professional bodies in the therapeutic goods legislation.

A member sought confirmation of whether information on the abovementioned reforms was publicly available and it was confirmed that this was the case.

6.2 Regulatory reforms update

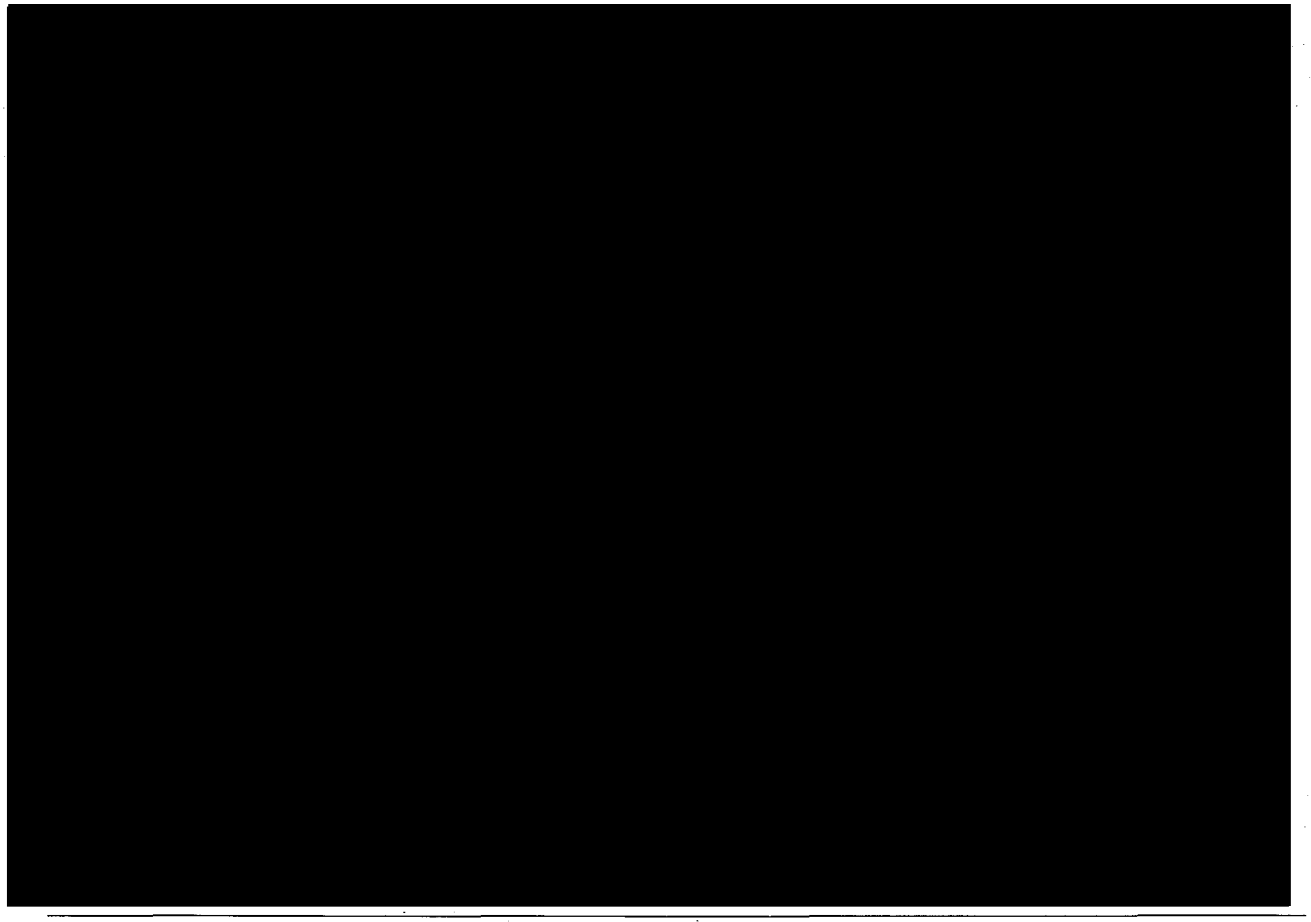
A TGA officer gave a presentation updating the members on the TGA blueprint reforms affecting complementary medicines, including updates to guidance documents (including the Australian Regulatory Guidelines for Complementary Medicines and the 'Evidence guidelines') and the 'permitted indications project'.

Members were advised of a recent series of 'road shows' that were conducted for external stakeholders regarding the current approach to evidence reviews of listed medicines and modifications that have been made to the Electronic Listing Facility

The members noted the publication of a list of newly cancelled listed medicines on the TGA website and discussed the amount of information that can be provided to external stakeholders in relation to these medicines.

6.4 Excipients that affect bioavailability of active ingredients – an update

Conflicts of interest



[redacted]

Background

A TGA officer introduced this item, reminding members of previous ACCM consideration of bioavailability enhancing excipients (at ACCM 10). Members were informed of two recent listing compliance reviews that provided insight into use of the ingredients in listed medicines and also the TGA recognition of a 1995 JECFA recommendation of an acceptable daily intake limit of 5 mg betacyclodextrin/kg body weight.

The members raised a question of whether bioavailable excipients are becoming increasingly common and a TGA officer confirmed that this appeared to be the case.

One member proposed that it should be recognised that betacyclodextrin is not inert and is beneficial in improving the bioavailability of active ingredients. This led to a discussion of the basic mechanisms by which it increased bioavailability and whether appropriate bioavailability studies would have been conducted when medicines are being formulated with these types of ingredients. While the answer to this question was not known, members noted that other changes to dosage forms may also affect bioavailability – such as use of micellular delivery systems.

The issue of receiving an altered or higher dosage as a result of enhanced bioavailability was raised and that better bioavailability does not necessarily mean increased safety or efficacy. This was well recognised in pharmaceutical formulations, but how analogous this was to complementary medicines was unclear.

[redacted]

7. Reports to ACCM

Nil

8. Other business

8.1 Feedback on current issues facing the TGA and complementary medicines

The Chair opened a discussion on the current issues affecting complementary medicines particularly in relation to the increased media attention that TGA has received. The members raised a question on how ACCM can contribute to the responses regarding the issues affecting the TGA. A TGA officer pointed out that the TGA has a communications team that monitors the media. There are times when the TGA has to respond within a short timeframe and this allows limited consultation from its pool of experts. The members requested to be kept up to date on the position of the TGA on various issues to align their responses to questions from the public. Members also requested updates on adverse events reported to the TGA and when consultations are published on the TGA website.

9. ACCM Committee Advice record

Advice 14.1

ACCM advises TGA that the submitted safety data package is not sufficient to establish safe use of citicoline in listed oral medicines. The committee acknowledges the extensive use of the substance in other jurisdictions, and the safety of choline but, in the absence of detailed use and adverse effect data and the outcome of the EFSA considerations, appropriate safety has not been established at this time.

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ACCM advises the TGA that given the context of wide use and its endogenous nature, glutathione is generally considered safe for use in oral listed medicines. However, the committee had concerns regarding potential confounding effects with other agents and its effect on melanin production which should be mitigated by a suitable advisory statement and a daily dose limit of 500 mg.

Chair's certification

I certify that this is an accurate record of proceedings of the meeting.

Professor Alan Bensoussan

ACCM Chair

10 December 2013

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