Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 6
Advisory Committee on Complementary Medicines

Extracted ratified minutes
Sixth meeting

3rd June 2011

TGA Health Safety Regulation

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADRs	Adverse Drug Reactions
ARTG	Australian Register of Therapeutic Goods
Deed Poll	Deed of undertaking in relation to confidential information and conflict of interest
OCM	Office of Complementary Medicines
ITM	Institute of Traditional Medicine
NNT	Number needed to treat
PPRC	*Pharmacopeia of the People's Republic of China*
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
26BB list	New legislative instrument for ingredients permitted in listed medicines

The Advisory Committee on Complementary Medicines (ACCM) held its sixth meeting at the Parkroyal Hotel, Melbourne Airport from 9:30 am to 4:00 pm on 3rd June 2011.

TGA note: This document is the extracted ratified minutes from the 6th meeting of the ACCM. The type of information that may have been removed from the full meeting minutes includes: discussion in relation to member's declarations of interests; information considered commercial in confidence or sensitive; action items; and matters still under consideration by the committee for which an outcome has yet to be determined.

Members of ACCM present

Professor Stephen Myers (Acting Chair)

Dr Lesley Braun

Ms Patricia Greenway

Ms Karen Martin

Dr Marie Pirotta

Dr Xianqin Qu

Dr Simon Spedding

Professor Peter Williams

Dr Hans Wohlmuth

Present from the Therapeutic Goods Administration

Ms Jenny Burnett (Secretary)

Mr Ian Stehlik (Office of Complementary Medicine Head)

Ms Diane Wilkinson

Present for part of the meeting

Dr Linda Lenton

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9:30am, welcoming ACCM members and TGA staff.

The Chair congratulated Mr Ian Stehlik on his appointment as Head of the Office of Complementary Medicines and Ms Jenny Burnett on her new role as Secretary of ACCM.

1.2 Apologies

Professor Alan Bensoussan

Professor Bill Webster

Dr Richard Oppenheim

Dr Megan Keaney

1.3 Verbal update on new conflict of interest forms, conflict of interest committee guidelines and new deed of confidentiality

A TGA officer introduced this item stating that all members should have received the following documents: the new 'Deed of undertaking in relation to confidential information and conflict of interest' ('Deed Poll'); the new 'Annual declaration of interests for members of TGA expert advisory committees' form; and the draft document 'TGA advisory committee guidelines: Declarations of interests, managing conflicts of interests and confidentiality obligations'.

In order to participate in committee business, all members are required to have a signed Deed Poll. Members were reminded that the original 'Deed Poll' contained an indemnity from the member to the Commonwealth for liability, losses and claims incurred resulting from any failure to comply with those obligations. The revised Deed Poll does not contain such an indemnity and members who have signed the previous Deed Poll are being given the option to sign the revised form. If a member chooses to sign the new Deed Poll, the obligations contained in that Deed Poll will apply from the date the new form is signed and duly witnessed.

Members commented that in the past it had been unclear what coverage or assistance would be given to committee members from the Government in the event of legal action, which had been a cause of concern for individuals. It was noted that under recent amendments to the TGA's insurance policy with the government insurer, Comcover, members of TGA's external advisory committees are provided cover for liability and professional indemnity in relation to their work on the committee.

Outcome

Members noted the new conflict of interest forms, conflict of interest committee guidelines and the new Deed Poll.

1.4 Conflict of interest

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

2. Confirmation of draft minutes of ACCM 5 (3 March 2011)

Discussion

A member commented on the length of the meeting minutes and questioned if it was necessary for the background information to be so detailed, suggesting that the minutes just refer to the briefing paper included in the agenda papers. A TGA officer responded that the minutes were useful as 'stand alone' documents when referenced within the TGA, and a comprehensive background reduced the need to refer back to (potentially) numerous briefing papers of previous meetings. Other members agreed, commenting that where agenda items were complicated and carried over numerous meetings, a comprehensive background in the minutes provided useful context for further deliberations.

Recommendation 6.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 5 (3 March 2011), as amended, are a true and accurate record of that meeting

3. Action arising from previous meetings

3.1 *Dictamnus dasycarpus* update

A TGA officer introduced this item, reminding members that they had considered possible safety concerns associated with the herbal species *Dictamnus dasycarpus* at ACCM 5 (March 2011). The safety concerns originated from multiple reports in Britain in the 1990s of liver damage associated with Chinese herb formulations (including *D. dasycarpus*) used to treat eczema and psoriasis. Further, in 2003 the Institute of Traditional Medicine (ITM) (Oregon, USA) reported a potential association with *D. dasycarpus* and rare, but serious, cases of liver reactions. Subsequently the herb was removed from formulations produced for the ITM. In 2010, the ITM released an alert after observing an increased number of literature reports of adverse liver reactions associated with *D. dasycarpus.*

At ACCM 5, members noted two Korean papers of interest and requested a translation or English data extraction of these papers to aid the committee's consideration. At ACCM 6, members were provided with English data extractions of these papers.

- A 2008 Korean article by Jang *et al.,* described four cases of toxic hepatitis that occurred several days after the patients consumed a decoction *of D. dasycarpus* root five to six times per day. The four patients had a median age of 60 years, common symptoms of jaundice and general weakness, and stated that they had not consumed alcohol for at least 5 years. The report concluded that *D. dasycarpus* induced liver injury presenting with a benign course lasting less than 1 month after cessation of the causative agent.
- A 2010 Korean article by Jung *et al.,* published in *The Korean Journal of Hepatology* described a study of the medical records of 28 patients diagnosed between 2003 and 2008 with acute toxic hepatitis following ingestion of preparations of *D. dasycarpus*. The biochemical pattern of liver injury was hepatocellular predominant and all patients recovered with supportive treatment.

Members were reminded that there are currently 28 medicines in the ARTG that contain preparations of *D. dasycarpus*. There have been four adverse drug reactions (ADRs) reported in Australia associated with medicines containing preparations of *D. dasycarpus* between 2003 and 2007, two of which were liver related, one was kidney related and the last event was an exacerbation of psoriasis.

Members were asked to provide comment on potential safety concerns for the herbal species *D. Dasycarpus.*

Discussion

A member drew the committee's attention to an article by D. Shaw published in *Planta Med* 2010 entitled 'Toxicological risks of Chinese herbs' which noted reports of hepatotoxicity for *D. dasycarpus* but the author concluded that there was no scientific or clinical evidence for this effect.

Data extraction of Korean articles

Members considered that the English data extractions provided for the two Korean papers did not give an indication of the quality of the data. Among the issues identified with the data extraction were: the causality of the ADRs was not clear; information on concomitant drugs was not provided; no quality rating was assigned to the papers; details of the plant part and preparations were not provided; and the nature of the hepatitis was not clarified for each patient.

For the twenty eight patients described in the 2010 article by Jung *et al.,* members commented that it is not clear if these ADRs are associated with the same product or preparation. As it was not clear what was taken, it is not possible to know whether there are issues relating to plant part, preparations or contamination.

ADRs reported in Australia

It was noted that the two ADRs associated with liver toxicity reported in Australia involved the same product. It was reiterated that adverse events are, in general, underreported and the fact that not many have been reported cannot lead to the assumption that there have not been many adverse events.

Appropriate plant parts based on traditional use

Members noted that the Jang *et al.* 2008 paper describes ADRs to a preparation of boiled 'root' consumed 5 to 6 times daily, while the Pharmacopeia of the People's Republic of China (PPRC) refers to ' root bark' as the traditional plant part used. Members discussed whether the adverse events could be attributed to the 'whole root' being used (although, it is not totally clear from the paper if this is the specific plant part used), rather than the PPRC recommended plant part, 'root bark'. It was also noted that the dose reportedly consumed in these cases was much higher than traditionally indicated in the PPRC.

This led to a discussion on different plant parts and preparations having very different chemical profiles. In relation to the current medicines on the ARTG containing *D. dasycarpus*, it was noted that the preparations of the herb included in these medicines were different to those associated

with ADRs in the two Korean papers. The importance of distinguishing between ADRs associated with decoctions from those associated with manufactured dosage forms was noted.

In general, members agreed that there was a need to increase knowledge relating to Traditional Chinese Medicine (TCM) issues. In particular, it was important that herbal medicines used as per the TCM paradigm were based on the plant parts and preparations used traditionally.

Members were reminded that when the list of permitted ingredients in listed medicines was initially established, herbal species were not restricted to plant parts or preparations. However, as new herbs are being approved for use in listed medicines, restrictions on plant parts and preparations are being included in the ingredient rules. To address the issue of 'grandfathered' herbal ingredients being unrestricted (with respect to plant parts), a TGA officer informed members that in the development of a new legislative instrument for ingredients permitted in listed medicines (the '26BB list'), restrictions were being placed on herbal species that have plant parts with a known safety concern. Where possible, use was also being restricted to those plant parts with a known safety profile. Members noted this with interest and requested an update on the development of the 26BB list at the next ACCM meeting.

As an aside, a member commented that there used to be a standing item on the agenda for the safety of herbal ingredients and questioned why this was no longer the case. A TGA officer responded that this agenda item related to an OCM project to review a list of herbal ingredients identified with potential safety concerns and this specific project had been completed. That given, where the TGA is aware of safety concerns relating to herbal ingredients that require advice from ACCM, this will be referred to the committee under general 'safety reviews'.

Nomenclature

To further complicate the issue, a member noted that the taxonomic classification of *Dictamnus* was in a state of flux, with the Kew Gardens Plant list stating the correct nomenclature as *Dictamnus alba*. Therefore, any consideration of ADRs relating to *D. dasycarpus* should also include *D. alba.*

Consumer concerns

Concern was raised in relation to the possibility of consumers purchasing preparations of *D. dasycarpus* over the internet, as in this case it was unlikely that the consumer would know what plant part or preparation is used in the medicine. The issue of counterfeit, unregulated medicines was also raised, given that for some countries counterfeit medicines may constitute up to 50% of medicines in the marketplace.

This led to discussion on the type of person who uses complementary medicines and would most likely purchase medicines over the internet. A member stated that surveys had indicated that the highest users of complementary medicines are well-educated females – a group of consumers that one could assume would be well informed.

Members considered it likely that the practice of purchasing medicines over the internet was increasing and questioned if there were any figures available to indicate how commonplace this practice is. A Member responded that the extent to which medicines are purchased over the internet is unknown, as this type of consumer operates on an individual basis and purchasing patterns are difficult to monitor. Another member informed the committee of a National Census undertaken approximately 3 years ago that determined that 2.3% of Australians aged over 50 years purchased medicines over the internet. The member added that the census is scheduled to be repeated in Australians aged less than 50 years, with the expectation that this age group will have a larger percentage of individuals purchasing medicines over the internet.

Members questioned whether consumers could be advised to not purchase medicines over the internet. A TGA officer informed members that there is a statement on the TGA website advising consumers to exercise extreme caution when purchasing medicines over the internet as products purchased in this way may not meet the same standards of quality, safety and efficacy as those approved by the TGA for supply in Australia, and may contain unauthorised and potentially harmful ingredients.

Communication with practitioners

It was noted that the majority of TCM medicines would be extemporaneously prepared by practitioners and therefore exempt from regulation. These may pose a greater risk to consumers,

rather than the formulated medicines on the ARTG which usually contain significantly lower doses. However, a member added that TCM practitioners should be aware of any potential safety concerns and it is unlikely they would prescribe preparations of *D. dasycarpus* to patients with liver conditions.

While the TGA does not regulate practitioners, it was noted that TCM is moving to National Regulation next year. Members agreed that it was important that TCM practitioners be aware of potential safety concerns with this herb and suggested that the Victorian Registration Board might provide a useful conduit to alerting TCM practitioners.

Insufficient evidence

Members noted that, while the ITM had highlighted a potential risk associated with the *D. dasycarpus,* the herb was commonly used, had a long traditional history of use and there did not appear to be a biologically plausible mechanism for liver toxicity.

The committee presumed that the ADRs reported in the literature were idiosyncratic hepatic reactions, which are different to instances of direct acute toxicity. A wide range of substances are associated with idiosyncratic hepatic reactions and genetic variability can affect a person's susceptibility to these reactions.

While there have been 28 cases of adverse liver reactions reported for the herb, this should be considered in context with how many doses have been consumed over this period of time. For a commonly used herb with widespread traditional use, 28 ADRs spread over millions of doses would equate to a relatively small incident rate.

Members were not convinced, based on the available information, that there was evidence of a high risk of hepatotoxicity. Given that there is insufficient information, members considered that the safety of the herb should be monitored on a watch list.

The ACCM considered that sponsors, consumers and practitioners would benefit from information on this issue. In particular, consumers and TCM practitioners using raw materials should be made aware of potential safety concerns associated with the use of *Dictamnus* species. A Member further questioned if they would be at liberty to discuss the safety concerns raised in relation to *Dictamnus* species with other TCM practitioners. It was considered that this would be acceptable, as the committee's deliberations on the matter would be available in the public domain when the committee's extracted ratified minutes were published on the TGA website.

Range of regulatory options and the role of ACCM

It was noted that the committee has worked on a number of complex issues over time (e.g. kava and black cohosh), for which different levels of regulatory action have been initiated by the TGA. Members questioned what range of regulatory options are available to the TGA to address potential safety concerns associated with complementary medicines (e.g. letters to sponsors, label warnings, information on website, statement to practitioners, a message in the ADR bulletin, or direct communication with manufacturers and associations), adding that a guidance document describing these would be useful for ACCM when considering such matters.

A member commented that the name of the ACCM (previously the Complementary Medicines Evaluation Committee) had been changed from an 'evaluation' committee to an 'advisory' committee and questioned what that entails. That is, how, what and who does the committee advise? The committee also sought clarification of how ACCM interacts with the OCM and the TGA in relation to issues and recommendations. The committee also questioned what role they could play in educating the public, comparing the TGA with other organisations, such as the Food Standards Australia and New Zealand, which use a variety of communication mediums, such as email and "tweets".

A TGA officer commented that this debate was timely, given that reviews of TGA transparency and complementary medicines were currently in process. In addition, a revised TGA website had recently been launched, making it much easier for consumers, industry and healthcare professionals to access information.

Outcome

Members considered, based on the available information, that there did not appear to be a serious safety concern associated with the use of the herbal species *Dictamnus dasycarpus*. However, the TGA should continue to monitor any further information that arises in association with use of this herb.

4. Guidelines on levels and kinds of evidence to support claims

Nil items

5. Evaluation of new substances

Nil items

6. Safety or efficacy reviews

Nil items

7. Registration applications

7.1 Registration application for a product containing *Pelargonium sidoides*

Background

A TGA officer introduced this item reminding members that, at ACCM 5 (March 2011) they had considered a registration application for a new product, Kaloba®, which contains an extract of *Pelargonium sidoides* root as the active ingredient. The proposed indications are for the treatment of acute bronchitis in adults and children and acute sinusitis in adults. At the March meeting, the committee appeared satisfied that safety was established, but a number of issues concerning the quality and efficacy of the product were raised by members both at that meeting and out of session. To address these concerns members were provided with relevant published studies, a Cochrane review and the applicant's response addressing the committee's previously raised concerns.

With respect to the efficacy aspects of the application, members were advised that the pivotal clinical trials included two studies each in adults and children for acute bronchitis and one study for acute sinusitis in adults, all of which were randomised, placebo-controlled, double-blind, multi-centre, parallel group studies. All of these studies used the same well-matched placebo, and randomisation appears to have been conducted appropriately. All studies employed a group sequential adaptive design, which is not ideal, but appropriate measures were in place so that double-blinding was preserved at the interim analyses, in accordance with relevant international guidelines. In relation to the use of co-medication, the applicant clarified there appears to be no significant difference between treatment and placebo groups. The trials were of a reasonable size, with the numbers of subjects treated with Kaloba® ranging from around 50 to 100 (if the different age groups in the children's studies are considered together).

However, the trials utilised a relatively large number of centres, ranging from 6 in the adult bronchitis studies to 11 in the acute sinusitis study. Also on the negative side, the primary endpoints of change in bronchitis or sinusitis symptom severity score, were based on non-validated instruments, but members noted that there are no 'gold standard' diagnostic criteria or validated scores for these illnesses. In their response, the applicant argued that the subjective symptom scores represent useful diagnostic tools for following change in symptoms during clinical trials, and that objective measures such as pulmonary function testing are not generally used in the diagnosis of acute bronchitis. The applicant also provided additional information on the question of the severity of the acute bronchitis that the subjects exhibited. It appears that the proportion of subjects with more severe bronchitis symptoms may have been quite variable between the studies.

At ACCM 5 members had questioned the statistical analyses, given that the 'p' values appeared to be remarkably low, and figures such as number needed to treat (or NNTs) were generally not provided. In 'out of session' consideration of the calculation of NNTs, it became apparent to

members that the primary endpoints did not lend themselves to such a calculation, so the suitability of these endpoints also came into question. In response, the applicant provided NNT calculations, but for secondary outcome measures which represent pre-defined response criteria based on the symptom scores. Members noted that all of these NNT calculations were quite low.

With regard to criticism of the suitability of the primary endpoint, it was noted that for the Cochrane review, the authors requested additional information from the manufacturer in order to facilitate the meta-analysis. This included the number of subjects with complete resolution of all symptoms and individual symptoms. Based on this information, the review concluded that *P. sidoides* may offer symptom relief for acute bronchitis in adults and children and acute sinusitis in adults, but the clinical relevance of this effect was uncertain. The review authors also concluded that all of the pivotal studies (included in the current TGA registration application) had acceptable methodologies for inclusion in the meta-analysis and were categorised as having a moderate risk of bias.

Finally, also in relation to the statistical analyses, the influence of the different study 'centres' on the overall primary outcome measures was questioned by members. The applicant claimed that though there is variability between the centres in each of the studies in relation to the primary outcome variable, there was no single site that dramatically influenced the overall result.

Discussion

The Chair reminded members that this was an application for a registered complementary medicine and safety, quality and efficacy were required to be demonstrated. Members had been satisfied at ACCM 5 that safety had been demonstrated, it was now necessary for the committee to be satisfied with the evidence supporting efficacy and quality.

Quality

Members considered the applicant's justification that polyphenols represent the quantitatively most important components in the extract and, as such, are suitable for use as marker compounds. Members acknowledged the difficulty in selecting a marker compound, given that the active constituents were not known. However, *P. sidoides* is not a herbal material where the chemistry is poorly understood and it was considered that a standard component or a therapeutic marker should have been identified. Some members remained unconvinced that the use of a universal non-specific assay for all polyphenolic compounds was adequate, as this methodology is 20 years out of date and provides a crude measure of the total amount of polyphenols, not the changes occurring within the suite of coumarin compounds. The coumarins could be measured by a method such as high-performance liquid chromatography, given that most facilities would have this technology available. Further, a member stated it was possible for the herbal material to be adulterated with a closely related species, *Pelargonium reniforme,* and questioned how the current analytical method could distinguish between the two species (without using a marker compound) as both species contain coumarins.

A TGA officer commented that while the universal non-specific assay for all polyphenolic compounds was a crude quantitative measure, and probably not suited for use as a definitive identification test, it was sufficiently sensitive to detect a downward trend in the polyphenol content. As a result, this methodology could be considered a valid assessment of the stability of the extract and the arbitrary selection of a particular marker may not provide a more meaningful measure of on-going quality.

Members noted that the product had been available in Europe for 50 years and this method is probably what was used when the product was first registered and the manufacturer may see no reason to change their practice.

Members considered their concerns were in relation to quality (and associated efficacy) rather than stability. It was questioned whether, in the absence of a suitable marker, bioassays could be undertaken to demonstrate batch to batch variability, such as an anti-inflammatory curve.

Members noted that the data demonstrated that the substance had efficacy and a good safety profile, but the demonstration of quality was not ideal. However, it was agreed that it would be a unfortunate for the medicine to not be available in Australia based on this issue alone, given that herbal materials are complex substances and are not always well characterised.

Members questioned how a changing evidence base is monitored after a medicine has been included on the ARTG. On-going responsibilities for sponsors to hold stability data was noted.

Efficacy

In general, members were impressed by the researcher's comprehensive explanation of the clinical trials.

It was noted that there were five studies included in the Cochrane review: two in children, two in adults and one in adults with acute sinusitis. All studies were performed in Eastern Europe by the manufacturer and had not been replicated in other regions. The evaluation of the effects of the medicine in adult patients with acute rhinosinusitis was based on a single unpublished study which had shown significant treatment effects for the resolution of all symptoms.

In relation to the study on acute rhinosinusitis, a member provided the end points re-calculated as percentages. The treatment reduced symptoms by 80%, whereas the placebo reduced symptoms only by 52%, which was statistically, but not clinically, significant. The Cochrane review concluded that if *P. sidoides* is to have a role in the symptomatic treatment of patients with acute rhinosinusitis, the study results should be replicated and efficacy needs to be confirmed using more valid endpoints. The committee concurred with this conclusion.

A member questioned what level of evidence is required to demonstrate efficacy for a complementary medicine and whether a medicine can be registered on the basis of one study. The member continued that, given that complementary medicines are, in general, low risk, a lower level of evidence should be acceptable. The efficacy of *P. sidoides* has been demonstrated *in vivo* and, while there was only one study on acute sinusitis, it had been well conducted and the results biologically plausible with the substance having multiple mechanisms of therapeutic activity. It was noted that demonstrated biological mechanisms are not often included in submissions. Consistent with the Australian Regulatory Guidelines for Complementary Medicines, this application was based on a randomised controlled trial supported by a plausible mechanism. While it would be preferable that more studies be available, it was recognised that, in general, the research available for complementary medicines was not vast and one good study is often all there is.

A TGA officer informed members that, in fact, there had been another study in adults in acute sinusitis. The second study used half the dose, which had not been efficacious and hence had a high dropout rate.

It was noted that the medicine was indicated for short term treatment and had a low side effect profile. Members noted that the proposed medicine may provide a better risk/benefit profile than the pharmaceutical medicines currently available for the treatment of coughs and colds and the limited amount of clinical data may not be of critical importance. It was agreed that it is not in the best interest of consumers to deny access to a potentially beneficial, low risk medicine because the level of evidence required is unreasonably high.

A member questioned the inclusion of the word 'may' in the Cochrane review's conclusion: "*P. sidoides may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults*". Another member explained that the use of the word 'may' was commonly included in Cochrane conclusions to prevent the statements being definitive, as they can only be a representation of the current available evidence.

A TGA officer stated that the committee had been provided with all the information that is currently available and advised that the current discussion could only be based on this information. The committee considered that the efficacy for the medicine had been adequately demonstrated, however, clarified that this is based on only one study in rhinosinusitis and should be reviewed if evidence changes.

In general, Members considered that the TGA should investigate the process for reviewing indications as the body of evidence changes.

Indications

A TGA officer informed the committee that the indications for the medicine were for sinusitis in adults and acute bronchitis and sinusitis in children over 2 years, which had been supported by the clinical evaluator.

Members questioned the inclusion of 'acute' bronchitis in the indications for the medicine, considering it may be more accurate to state 'mild to moderate' bronchitis, given that the individuals included in the clinical trials had not been adequately demonstrated to be suffering severe bronchitis. To establish efficacy for this condition, a clinical trial involving a large sample of subjects with severe bronchitis should be conducted.

Another member contested that the severity of bronchitis was difficult to assess, given that most cases would improve after 7 days without treatment. In conventional medical treatment, if the condition lasted longer than 10 days, then antibiotics would be prescribed. However, studies have shown that the benefit of antibiotics is minimal, only making a half day difference to recovery and not affecting the severity of the symptoms. Further, distinguishing between mild, moderate or severe bronchitis would not be meaningful to consumers and it is unlikely that such a distinction would prevent consumers with severe bronchitis from taking the medicine.

Given that the standard medical treatment is to wait until symptoms have been around a considerable time before antibiotics are prescribed, members agreed that Kaloba®, containing the active ingredient *P. sidoides,* will do no harm and may, in fact, offer relief for conditions where there are few alternative effective treatment options available.

Label advisory statements

Members agreed the proposed label advisory statement '*consult with your doctor if no improvement, fever, short of breath, bloody sputum and not under 2 years of age*' was appropriate, and adequately informed consumers of symptoms of concern e.g. those symptoms that may indicate the person is suffering from a more serious condition, such as pneumonia.

Outcome

Members considered that safety and efficacy had been demonstrated for the medicine. In relation to quality, members considered that the data provided to support this was adequate, although the methodology used was of the minimal acceptable standard.

Recommendation 6.2*

ACCM recommends to the TGA that Kaloba®, containing the active ingredient *Pelargonium sidoides*, has demonstrated a sufficient level of evidence in support of the safety, quality and efficacy required for a registered complementary medicine.

Having given consideration to the totality of evidence and the ratio of risk to benefit for the product, ACCM considers that the level of evidence is sufficient to support the following indications:

- Treatment of acute bronchitis in adults.
- Treatment of acute bronchitis in children over 2 years (with medical supervision for children less than 6 years of age).
- Treatment of acute sinusitis in adults.

**TGA note: Whether or not an application is approved is a decision made by a delegate of the Secretary under the relevant provisions of the Therapeutic Goods Act 1989. The advice provided by the ACCM is only one of the many matters a delegate may need to take into account in making their determination on whether or not to approve an application. It should not be assumed that the decision of the delegate will reflect the opinion of the committee.*

8. Regulatory reforms

8.1 Verbal report on the working group to review complementary medicine regulation in Australia

Background

A TGA Officer introduced this item advising members that there were currently a number of TGA reviews in progress including: a review to improve the transparency of the TGA; an advertising

review (including a review of the complaint resolution process); an organisation performance review by the Australian National Audit Office; and a review of the regulation of complementary medicines. A common theme arising from these reviews is the need for the TGA to be more transparent and improve communication with its stakeholders.

The officer noted that a working group had been convened by the TGA to assist in the review the regulation of complementary medicines. Members were reminded of an expert advisory panel review of complementary medicines that occurred in 2003, which resulted in 14 recommendations. The working group has discussed the progress that had been made in implementing these recommendations.

Members questioned how ACCM could be involved in the strategic planning for reform. The officer responded that the TGA welcomed the committee's input. The key role of the committee is advising on the safety and quality of complementary medicines, contributing valuable advice to increase the effectiveness of the regulator.

Outcome

Members noted the progress of the working group established to review complementary medicine regulation in Australia. Members requested that, if possible, a report from the working group be made available to ACCM.

9. Adverse drug reactions associated with complementary medicines.

9.1 ADRs associated with complementary medicines from 1 February 2011 to 31 April 2011

Discussion

ACCM noted the adverse drug reactions (ADRs) reported for complementary medicines from 1 February 2010 to 31 April 2011.

Members discussed that, in general, ADRs are underreported. It was estimated that, for pharmaceutical medicines, only 10% of ADRs are reported and it was assumed that this figure would be even lower for complementary medicines. A member informed the committee that a census undertaken in patients over 50 years of age indicated that only 9% accessed medicines through a practitioner, while 50% accessed medicines through a health food shop. This indicates that the majority of complementary medicines are self prescribed and minor adverse events in this group are unlikely to be reported. Another member spoke of a similar study they had been involved in, which revealed that, from 800 patients who had experienced an ADR to a complementary medicine, the majority did not report this to anyone, mostly because the ADRs were minor, of short duration and reversible. With more severe ADRs, a person might tell their doctor, health care practitioner or a pharmacist.

In addition to underreporting by consumers, a member commented on a misconception amongst some complementary healthcare practitioners that their access to herbs will be restricted if ADRs are reported. This highlighted the need for education of practitioners to break down the misconceptions, fear and distrust of medicine regulation. Collaboration was also required with the complementary medicine industry and it was suggested this might be achieved through discussions with the peak industry bodies.

It was agreed the issue of underreporting for ADRs was of broader concern and ACCM requested they be briefed on the TGA's pharmacovigilance program.

Outcome

Members noted the ADRs associated with complementary medicines from 1 February 2011 to 31 April 2011.

10. Matters referred from within TGA

10.1 Article on potential safety concern for phytosterols

Background

A TGA officer introduced this item, asking members to note an article by Danesi *et al.,* entitled 'Phytosterol supplementation reduces metabolic activity and slows cell growth in cultured rat cardiomyocytes' published in the *British Journal of Nutrition* in 2011.

In this study, primary, non-neoplastic neonatal rat cardiomyocytes were supplemented with two different phytosterol concentrations (3 or 6 mg/ml), both within the range of human plasma concentration. Cardiac cells were chosen as an experimental model as the heart has been reported as the target organ for subchronic toxicity of phytosterols. The study demonstrated that phytosterols caused a reduction in metabolic activity (measured as 3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) conversion) and a slowing down of cell growth in the rat cardiomyocytes.

The authors concluded that the lower MTT conversion and the similar lactate dehydrogenase release suggested that phytosterols target mitochondria rather than plasma membrane integrity. The authors considered that the replacement of cholesterol by phytosterols could also have caused the observed slowing down of cell growth and the reduction in metabolic activity, which could rely on the phytosterols increase, cholesterol decrease, or both. While the authors acknowledge that it is difficult to translate the obtained results to the health of human heart tissue, they consider that the demonstration of decreased cardiac cell growth and decreased metabolic activity induced by phytosterols raises concerns about the safety of long-term exposure to physiologically relevant phytosterol concentrations.

ACCM noted that there are currently three phytosterol-based ingredients permitted for use in listed medicines:

- Phytosterol complex – conifer
- Omega-3 fish oil phytosterol esters
- Vegetable oil phytosterol esters

ACCM was asked to advise if this study raised any safety concerns for listed medicines containing phyosterol-based ingredients.

Discussion

Members noted that the study (Danesi *et al.,* 2011) used high doses of phytosterols on cardiac cells. The Commitee agreed it is difficult to translate this data to oral doses of phytosterols in humans, given that phytosterols are not well absorbed. It was necessary to know what the oral dose would be to achieve the same plasma levels. At best, this article could only raise a theoretical issue.

As an aside, members noted that there is a significant focus on lowering cholesterol as a risk factor for cardiovascular disease. However, this is only one risk factor of the disease. Other, perhaps more significant factors include stress, obesity and lifestyle.

Outcome

ACCM noted the recent article on phytosterols by Danesi *et al.,* but considered that this study does not raise cause for concern for listed medicines containing phytosterol-based ingredients.

11. For information

11.1 Medicines Safety Update No 2 bulletin 2011

Outcome

Members noted the Medicines Safety Update No 2 bulletin 2011.

11.2 Advisory Committee on Medicine Safety minutes meeting No 5

Outcome

Members noted the Advisory Committee on Medicine Safety Meeting No 5 Minutes.

11.3 Advisory Committee on Medicine Safety minutes meeting No 6

Outcome

Members noted the Advisory Committee on Medicine Safety Meeting No 6 Minutes.

12. Sponsor representations to ACCM

Nil items.

13. Other business

13.1 Proposed meeting dates 2012

Background

Members were asked to consider the following dates for ACCM meetings in 2012.

9 March 2012

1 June 2012

7 September 2012

7 December 2012

Outcome

Members noted the proposed meeting dates 2012

14. Recommendation Record

Recommendation 6.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 5 as amended, are a true and accurate record of that meeting.

Recommendation 6.2*

ACCM recommends to the TGA that Kaloba®, containing the active ingredient *Pelargonium sidoides*, has demonstrated a sufficient level of evidence in support of the safety, quality and efficacy required for a registered complementary medicine.

Having given consideration to the totality of evidence and the ratio of risk to benefit for the product, ACCM considers that the level of evidence is sufficient to support the following indications:

- Treatment of acute bronchitis in adults.
- Treatment of acute bronchitis in children over 2 years (with medical supervision for children less than 6 years of age).
- Treatment of acute sinusitis in adults.

* *TGA note: Whether or not an application is approved is a decision made by a delegate of the Secretary under the relevant provisions of the Therapeutic Goods Act 1989. The advice provided by the ACCM is only one of the many matters a delegate may need to take into account in making their determination on whether or not to approve an application. It should not be assumed that the decision of the delegate will reflect the opinion of the committee.*

The Chair closed the meeting at 4.40pm.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au