EDITED SUBMISSIONS RECEIVED IN RESPONSE TO THE NOTICE INVITING SUBMISSIONS ON MATTERS REFERRED TO THE:

Advisory Committee on Chemicals Scheduling – 18 October 2011 (ACCS#3);
and
Advisory Committee on Medicines Scheduling – 19 October 2011 (ACMS#4).

Regulation 42ZCZL, Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary of the Department of Health and Ageing publishes herein all valid public submissions made in response to the invitation contained in the notice inviting public submissions for ACCS#3 and ACMS#4 (the October 2011 meetings), with the closing date of 7 September 2011.

In accordance with the requirements of subsection 42ZCZL of the Regulations these submissions have been edited to remove information that a delegate considers to be confidential.

As advised in the notice inviting public submissions, it was up to the person making the submission to highlight any information which they wished to request be considered as confidential. Material claimed to be commercial-in-confidence has been considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework (SPF), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Discrete submissions have been grouped by item. However, a number of applicants provided submissions that related to multiple items. These submissions on multiple items have been separately grouped.

LIST OF SUBMISSIONS

1. ACCS #3

Item	Number of public submissions
1.1 Ametoctradin	1 (and in 1 submission under item 1.7)
1.3 Fluxapyroxad	1 (and in 1 submission under item 1.7)
1.6 Dicamba	1 submission under item 1.7
1.7 Submission on multiple items	1

2. ACMS #4

Item	Number of public submissions
2.2.1 Azelastine	4 (and in 1 submission under item 2.4)
2.2.2 Diclofenac	1 (and in 1 submission under item 2.4)
2.2.3 Famciclovir	1 (and in 1 submission under item 2.4)
2.2.5 MDPV	1 submission under item 2.4
2.2.6 Synthetic cannabinoids	6 (and in 1 submission under item 2.4)
2.2.7 Kava	2
2.3.1 Adrenaline	4 (and in 1 submission under item 2.4)
2.4 Submissions on multiple matters	2

[redacted]

1.1 Ametoctradin - submission 1 of 1.

5 September 2011

[redacted]

The Secretary
Scheduling Secretatiat
GPO Box 9848
Canberra ACT 2601
Australia
e-mail submission

Subject: Submission of Public Comments Regarding Scheduling Proposal for Ametoctradin to be Considered at the 18 October 2011 Advisory Committee on Chemicals Scheduling Meeting

Dear Secretary,

Your delegate has requested scheduling advice from the Advisory Committee on Chemicals Scheduling (ACCS) regarding ametoctradin, a new chemical currently under evaluation by the Australian Pesticide and Veterinary Medicines Authority for use as a fungicidal active ingredient. [redacted] would like to affirm our support for the following proposal made by the Australian Office of Chemical Safety and Environmental Health (OCSEH).

For ametoctradin, the OCSEH proposed listing in Apendix B of the Australian *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Thank you for your consideration of this information.

[redacted]

[redacted]

[redacted]

1.3 Fluxapyroxad - submission 1 of 1.

5 September 2011

[redacted]

The Secretary
Scheduling Secretatiat
GPO Box 9848
Canberra ACT 2601
Australia
e-mail submission

Subject: Submission of Public Comments Regarding Scheduling Proposal for Fluxapyroxad to be Considered at the 18 October 2011 Advisory Committee on Chemicals Scheduling Meeting

Dear Secretary,

Your delegate has requested scheduling advice from the Advisory Committee on Chemicals Scheduling (ACCS) regarding fluxapyroxad, a new chemical currently under evaluation by the Australian Pesticide and Veterinary Medicines Authority for use as a fungicidal active ingredient. [redacted] would like to affirm our support for the following proposal made by the Australian Office of Chemical Safety and Environmental Health (OCSEH).

For fluxapyroxad, the OCSEH proposed inclusion in Schedule 5 of the SUSMP with no cut-off.

Thank you for your consideration of this information

[redacted]

[redacted]

[redacted]

07 September 2011

1.7 Multiple matters - submission 1 of 1.

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Email: SMP@health.gov.au

Dear Sir

Public Comment submissions to 18 October 2011 meeting of the Advisory Committee on Chemicals Scheduling (ACCS)

We refer to the pre-October 2011 ACCS Meeting notice inviting public submissions with respect to certain substances, addressing a matter raised in s.52E of the Therapeutic Goods Act 1989.

[redacted] wishes to provide information for ACCS consideration for the matters/substances addressed in the attached submissions.

[redacted] with regard to the substances nominated in the submissions and would appreciate being advised of the Committee's considerations, with the opportunity for further submission, if appropriate.

We look forwards to ACCS's further advice. Should the committee require any additional information from [redacted]

Yours sincerely,

[redacted]

[redacted]

Advisory Committee on Chemicals Scheduling
Meeting: 18 October 2011

Agenda Item 1.1
Ametoctradin – Consideration of scheduling, including a proposed new entry in Appendix B or under Schedule 5

[redacted] notes the current proposal to classify ametoctradin as not requiring scheduling or as a Schedule 5 substance.

[redacted] This new molecule is being targeted for use in horticulture.

Public submissions that address matters mentioned in section 52E of the Therapeutic Goods Act 1989 have been invited.

S52E (1) (b) the risks and benefits associated with the use of a substance
The committee may take into account the risks and benefits associated with the use of a substance Section 52E (1) (b).

One of the great benefits of this new molecule is its contribution to resistance management. Diseases in agriculture can develop resistance quickly if the same chemistry is used multiple times in succession without the use of other chemistry. This new molecule lends its self to mixtures with existing chemistries which will delay the development of resistance (as two mode of action are being used in a combined spray). This will promote the longevity of other chemistries as well as bring new chemistry to the "tool box" for disease management in agriculture.

S52E (1) (d) the extent and patterns of use of a substance
The committee may take into account the extent and patterns of use of a substance Section 52E (1) (d).

This product functions to control oomycetes and is a mitochondrial respiration inhibitor and belongs to a new class of chemistry, the pyrimidylamines. [redacted]

S52E (1) (h) the purpose for which a substance is to be used
The committee may take into account the purpose for which a substance is to be used Section 52E (1) (h).

This product only functions as a protectant fungicide. This means that once a disease is present ametoctradin will not control the disease. Ametoctradin needs to be applied to the crop before the crop is infected with the disease and it will prevent the disease devastating the crop. It is therefore a protectant fungicide and not a curative fungicide. This will give it a set opportunity to be applied in the crop, but when disease is present it will not be used.

[redacted]

Advisory Committee on Chemicals Scheduling
Meeting: 18 October 2011

Agenda Item 1.3
Dicamba – Consideration of changing the cut-off from 20% to 50% between Schedule 5 and Schedule 6

[redacted] notes the current proposal to change the cut-off between Schedules for dicamba from 20% to 50%.

[redacted]

Public submissions that address matters mentioned in section 52E of the Therapeutic Goods Act 1989 have been invited.

S52E (1) (d) the extent and patterns of use of a substance
The committee may take into account the extent and patterns of use of a substance Section 52E (1) (d).

This product functions to control weeds by disrupting plant cell growth. It targets broadleaf weeds in the presence of grasses, which has made it ideal for use in cereal crops as well as turf and pasture situations. This specificity has also benefits of use in the home garden market and is routinely found in [redacted] formulations. It is used to control many weeds in many situations, alone or in mixtures with other herbicides (either co-formulations or spray tank mixture partners). The chemistry is fairly benign which supports the change to the cut-off between scheduling as proposed.

S52E (1) (h) the purpose for which a substance is to be used
The committee may take into account the purpose for which a substance is to be used Section 52E (1) (h).

This product functions only as a herbicide. It can be used in agriculture, home garden situations, and non-crop areas (i.e. pine tree plantations, turf or environmental control of weeds by council, land care groups etc).

[redacted]

Advisory Committee on Chemicals Scheduling
Meeting: 18 October 2011

Agenda Item 1.4
Fluxapyroxad – Consideration of scheduling as a Schedule 5, or possibly as a Schedule 6

[redacted] notes the current proposal to classify fluxapyroxad as a Schedule 5 substance, and seek advice on Schedule 6.

[redacted] his new molecule is being targeted for use in horticulture, but also could have a good fit with other chemistry in cereals.

Public submissions that address matters mentioned in section 52E of the Therapeutic Goods Act 1989 have been invited.

S52E (1) (b) the risks and benefits associated with the use of a substance

The committee may take into account the risks and benefits associated with the use of a substance Section 52E (1) (b).

One of the great benefits of this new molecule is its contribution to resistance management. Diseases in agriculture can develop resistance quickly if the same chemistry is used multiple times in succession without the use of other chemistry. This new molecule lends its self to mixtures with existing chemistries which will delay the development of resistance (as two mode of action are being used in a combined spray). This will promote the longevity of other chemistries as well as bring new chemistry to the “tool box” for disease management in agriculture.

S52E (1) (d) the extent and patterns of use of a substance

The committee may take into account the extent and patterns of use of a substance Section 52E (1) (d).

This product functions to control three of the four classes of fungal disease, so has a broad fit in horticulture. It can be used in vegetables, grapevines and topfruit. In mixtures with [redacted] it can be used in [redacted]. In mixtures with [redacted] it can be used in [redacted]. Overseas it is being developed for use as a cereal fungicide.

S52E (1) (h) the purpose for which a substance is to be used

The committee may take into account the purpose for which a substance is to be used Section 52E (1) (h).

This product is a new generation of carboxamide fungicide. There are several companies that are developing similar new generation carboxamide fungicides. This group of chemistry is solely for use as a fungicide, and can be considered in matters of agronomic fit to be similar to boscalid [redacted] which is one of the original carboxamide fungicides.

[redacted]

2.2.1 Azelastine - submission 1 of 4.

The Secretary
Medicines & Poisons Scheduling
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848
Canberra ACT 2601
Australia

To whom it may concern,

Re: Invitation for public comment - ACMS meeting, October 2011- Rescheduling of Azelastine hydrochloride topical ocular preparation containing 0.05 per cent or less of azelastine

I note that the Advisory Committee for Medicines Scheduling (ACMS) is considering an application to reschedule Azelastine hydrochloride, as a topical ocular preparation, from Schedule 3 Pharmacist Only Medicine to Schedule 2 Pharmacy Medicine according to the criteria that Azelastine hydrochloride content is 0.05 per cent or less of azelastine per dosage unit.

In my professional capacity, I believe Azelastine hydrochloride presented in this form fulfils the criteria for a Schedule 2 medicine and is clearly similar to nine other Schedule 2 topical ocular preparations currently approved in Australia for same or similar indications.

Azelastine hydrochloride presented in this form has been approved and available for over two years on the Australian market.

On the basis of Quality Use of Medicine and availability of a logical ocular preparation to consumers I support the rescheduling application.

[redacted]

[redacted]

2.2.1 Azelastine - submission 2 of 4.

The Secretary
Medicines & Poisons Scheduling
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848
Canberra ACT 2601
Australia

To whom it may concern,

Re: Invitation for public comment - ACMS meeting, October 2011- Rescheduling of Azelastine hydrochloride topical ocular preparation containing 0.05 per cent or less of azelastine

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In my professional capacity, I believe Azelastine hydrochloride presented in this form fulfils the criteria for a Schedule 2 medicine and is clearly similar to nine other Schedule 2 topical ocular preparations currently approved in Australia for same or similar indications.

Azelastine hydrochloride presented in this form has been approved and available for over two years on the Australian market.

On the basis of Quality Use of Medicine and availability of a logical ocular preparation to consumers I support the rescheduling application.

[redacted]

[redacted]

The Secretary
Medicines & Poisons Scheduling
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848
Canberra ACT 2601
Australia

To whom it may concern,

Re: Invitation for public comment - ACMS meeting, October 2011- Rescheduling of Azelastine hydrochloride topical ocular preparation containing 0.05 per cent or less of azelastine

I note that the Advisory Committee for Medicines Scheduling (ACMS) is considering an application to reschedule Azelastine hydrochloride, as a topical ocular preparation, from Schedule 3 Pharmacist Only Medicine to Schedule 2 Pharmacy Medicine according to the criteria that Azelastine hydrochloride content is 0.05 per cent or less of azelastine per dosage unit.

In my professional capacity, I believe Azelastine hydrochloride presented in this form fulfils the criteria for a Schedule 2 medicine and is clearly similar to nine other Schedule 2 topical ocular preparations currently approved in Australia for same or similar indications.

Azelastine hydrochloride presented in this form has been approved and available for over two years on the Australian market.

On the basis of Quality Use of Medicine and availability of a logical ocular preparation to consumers I support the rescheduling application.

[redacted]

[redacted]

Proposal

2.2.1 Azelastine - submission 4 of 4.

2.2 Azelastine – seeking advice on a proposal to reschedule azelastine from Schedule 3 to Schedule 2 when supplied in topical eye preparations containing 0.05% or less of azelastine.

[redacted] supports the proposal to re-schedule azelastine to Schedule 2.

[redacted]

Background

Allergy commonly attacks the conjunctival mucosa, as well as the nose, sinuses, upper airways and lungs. The ocular component may be the most common and initially the most prominent life-altering symptomatic complaint. Patients experiencing allergic conjunctivitis experience acute attacks of red, irritated eyes with an intense feeling of itching that results in tearing.[1]

Azelastine is a potent anti-allergic compound with histamine H1-receptor antagonist activity. It has a rapid onset of action, within 10 to 20 minutes, and up to 12 hours duration of action.[2] In addition to its high affinity for H1 receptors, azelastine's ability to modify several other mediators of inflammation and allergy contributes to its mechanism of action, placing it among the new generation of dual-acting anti-inflammatory drugs. As a second-generation antihistamine, its relative lack of central nervous system activity distinguishes it from first-generation antihistamines.[3]

It is currently included in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in:

- Schedule 2 (S2) – for preparations for nasal use
- Schedule 3 (S3) – in topical eye preparations (≤ 0.05%)
- Schedule 4 (S4) – other than for S2/S3 listing

Key Points

1. As a dual-action antihistamine, topical ocular azelastine outperforms other S2 topical products in treating allergic conjunctivitis.
2. Azelastine is well tolerated with minimal systemic absorption.
3. Azelastine has as good or better a safety profile as other S2 products available for treating allergic conjunctivitis.
4. Allergic conjunctivitis should be managed in a manner to promote access to professional advice when required. An S2 medicine facilitates access without the requirement for direct pharmacist counselling associated with supplying S3 medicines.

Comments

[redacted] has considered the proposal to reschedule azelastine topical eye preparations from S3 to S2 with particular reference to the following subsections of the *Therapeutic Goods Act 1989 – Section 52E (1)*:

(a) the risks and benefits of the use of a substance

- As systemic absorption of azelastine from topical ocular preparations is minimal, it is well tolerated, even in more vulnerable groups such as children and elderly patients.[4]

[redacted]

- Even though azelastine is more than 90% metabolised by CYP3A4 and CYP2D6, and to a lesser extent by CYP1A2, the low plasma concentration of azelastine after topical administration means a relatively low risk of drug interactions.[5]
- The most common adverse reactions are taste perversion and application site reaction. Although azelastine reaches the tongue via the lacrimal duct after ocular installation and has a bitter taste, this has not reduced compliance in patients who regularly use topical ocular azelastine products. Similarly, studies in long-term users have shown that application site reaction has not resulted in greater discontinuation of therapy than from placebo.[6]
- Azelastine has a category B3 listing for safety in pregnancy, which indicates limited data regarding human use but studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.[7] As an S2 product, this risk could be managed by appropriate labelling and referral to the pharmacist if needed.
- Because absorption from the eye is limited, azelastine would not be expected to cause any adverse effects in breastfed infants. This can be minimised by applying pressure to the tear duct after application.[8] As an S2 product, this risk can be minimised by effective pharmacy assistant training and referral to pharmacists for advice when needed.

(b) the purposes for which a substance is to be used and the extent of use of a substance

- Allergic conjunctivitis is extremely common, affecting up to 40% of the population. There is some suggestion that allergic conjunctivitis is becoming more common, perhaps due to increasing air pollution and cigarette smoking.[9]
- Mild allergic conjunctivitis (acute, seasonal or perennial) represents up to 98% of all cases of ocular allergy.[10] The main symptoms of allergic conjunctivitis are itching of the eye and surrounding tissues, lacrimation (tearing), red eye, foreign body sensation and oedema of the eye lids. It is usually bilateral and associated with other conditions such as rhinitis.[11]
- Histamine is one of the mediators released by mast cells after specific allergen binding to the IgE presented on the cell surface, contributing to the signs and symptoms of the immediate reaction characterising allergic conjunctivitis.[12] Topical antihistamines are common treatments for allergic conjunctivitis.
- The most widely used first generation ocular topical antihistamines are antazoline and pheniramine, administered in combination with vasoconstrictors to improve efficacy in providing symptom relief.[13] A number of S2 topical vasoconstrictor-antihistamine combination preparations are currently available for which rebound conjunctivitis is a risk with long-term use. With topical ocular vasoconstrictor use, it is recommended not to use regularly for more than 5 days.[14] These products are contraindicated in people with narrow-angle glaucoma and caution is advised for elderly people and people with severe cardiovascular disease, uncontrolled hypertension, uncontrolled diabetes and people with urinary retention or prostate hypertrophy.[15]
- Azelastine has been shown to effectively reduce allergic symptoms in patients suffering from seasonal allergic conjunctivitis, with a near maximal response after only 3 days of treatment.[16]
- Other topical second-generation antihistamines used for allergic conjunctivitis which have similar efficacy and safety profiles available as S2 products include:

[redacted]

    - Levocabastine (e.g. Livostin® Eye Drops)
    - Ketotifen (e.g. Zaditen® Eye Drops)
- As a second-generation antihistamine, azelastine has antihistaminic and anti-inflammatory properties. As a drug class, topical antihistamines with established dual action are very effective in treating allergic conjunctivitis and outperform other groups of drugs such as mast cell stabilisers or topical non-steroidal anti-inflammatory drugs.[17] In contrast to second-generation antihistamines, it has not been possible to demonstrate that first-generation antihistamines offer anti-inflammatory-anti-allergic action in addition to their anti-pruriginous effects.[18]

(c) the dosage, formulation, labelling, packaging and presentation of a substance

- Since the conjunctiva is an accessible mucosa, topical drug application is an ideal approach for the treatment of allergic conjunctivitis, since rapid action is assured, with improvement in eye hydration. Many studies have shown this administration route to be equally or even more effective than oral or nasal topical treatments.[19]
- Risks associated with use in pregnancy or inappropriate use can be ameliorated by including the following warnings on the label[20]:
    - 13 – Do not use if pregnant
    - 77 – If symptoms persist, seek advice from a health care practitioner
- In addition to appropriate label warnings, as a S2 product, pharmacy assistants are also trained to follow a protocol in asking questions to determine if referral to a pharmacist for professional advice is needed.

(d) other matters in public health interest

- Non-pharmacologic interventions including strategies to reduce exposure to inciting antigens, management of dry eye and even dietary intervention are essential components in the care of patients with ocular allergy. [21] Including ocular allergy products in S2 promotes access to intervention from pharmacists if required to assist with pharmacologic and non-pharmacologic advice.
- While S3 is more effective in facilitating pharmacist intervention, including products in S3 can have a significant impact on pharmacist workflow. Mandatory pharmacist intervention is warranted when there are safety concerns or difficulties in patients being able to differentiate conditions from the presenting symptoms. Otherwise, for products with a good safety profile and proven efficacy for non-serious conditions with easily identifiable symptoms, pharmacy assistants are capable of supporting the supply of S2 products with referral to the pharmacist when needed, for situations beyond their scope of practice.
- Pharmacy assistants must complete appropriate training regarding S2 and S3 medicines as part of the Quality Care Pharmacy Program (QCPP) accreditation and since April 2010, refresher training for pharmacy assistants, focused on applying S2/S3 professional supply protocols, has been needed for QCPP re-accreditation.

Conclusion

With a considerable number of topical ocular S2 products already available for the treatment of allergic conjunctivitis, [redacted] believes the safety and efficacy profile for topical azelastine is such that it does not warrant regular pharmacist intervention for

[redacted]

supply without a prescription. Pharmacy assistants are well trained to support the supply of azelastine as an S2 ocular product with referral to the pharmacist as required.

Reference Sources:

[1] PB Williams, E Crandall, JD Sheppard; Azelastine hydrochloride, a dual-acting anti-inflammatory ophthalmic solution, for treatment of allergic conjunctivitis; Clinical Ophthalmology 2010:4 993-1001
[2] Product Information, Eyezep, eMIMS, August 2011
[3] Op Cit; PB Williams
[4] Op Cit; PB Williams
[5] Op Cit; PB Williams
[6] GW Canonica, G Ciprandi, U Petzold et al; Topical Azelastine in perennial Allergic Conjunctivitis; Medscape 2003; http://www.medscape.com/viewarticle/458572
[7] http://www.tga.gov.au/hp/medicines-pregnancy.htm
[8] LactMed; Toxicology Data Network; www.toxnet.nlm.nih.gov
[9] Virtual medicine Centre – Allergic conjunctivitis; http://www.virtualmedicalcentre.com/diseases.asp?did=766&title=Allergic-Conjunctivitis
[10] Ibid
[11] Australian Society of Clinical Immunology and Allergy; http://www.allergy.org.au/content/view/186/1/
[12] A del Cuvillo, J Sastre, J Montoro et al; Allergic Conjunctivitis and H1 Antihistamines; J Investig Allergol Clin Immunol 2009; Vol 19, Suppl.1:11-18
[13] Ibid
[14] AMH – Vasoconstrictors (eye)
[15] Naphcon-A Full Product Information; eMIMS
[16] Op Cit; Medscape
[17] Op cit; A del Cuvillo
[18] Op cit; A del Cuvillo
[19] Op cit; A del Cuvillo
[20] Required advisory statements for medicine labels (September 2008); www.tga.gov.au
[21] Op Cit; PB Williams

[redacted]

[redacted]

7 September 2011

[redacted]

– 19 October 2011

2.2.2 Diclofenac - submission 1 of 1.

Proposal

2.3 Diclofenac - seeking advice on a proposal to exempt from scheduling topical preparations containing diclofenac, other than those indicated for the treatment of solar keratosis. Advice is also being sought on two alternative approaches to this possible exemption from scheduling:

- limiting this possible exemption to preparations containing 4 per cent or less of diclofenac, other than those for the treatment of solar keratosis; or
- an exemption for topical preparations containing 2 per cent or less diclofenac and including in Schedule 2 topical preparations containing more than 2 per cent, up to 4 per cent diclofenac, when not indicated for the treatment of solar keratosis.

[redacted] supports the following scheduling arrangements for topical diclofenac:

- Schedule 4 for products containing 3% of more diclofenac, irrespective of indications for use
- Schedule 2 or 3 for products containing from >1% and <3% of diclofenac, irrespective of indications for use

[redacted]

[redacted]

Background

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used for musculo-skeletal pain and inflammation. The adverse events associated from systemic NSAID therapy (oral or rectal) led to the development of topical formulations for local use with reduced adverse effects.

Diclofenac is currently included in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in:

- Schedule 2 (S2) – for divided preparations for oral use containing 12.5mg or less of diclofenac per dosage unit in a pack containing 10 or less dosage units and labelled with a recommended daily dose of 75mg or less of diclofenac
- Schedule 3 (S3) – for divided preparations for oral use containing 25mg or less of diclofenac per dosage unit in a pack containing 30 or less dosage units (except when included in S2)
- Schedule 4 (S4) – except when included in S2 or S3 or in preparations for dermal use unless used for the treatment of solar keratosis or containing more than 1% of diclofenac.

Products containing 1% diclofenac (equivalent to 1.16% diclofenac diethylammonium) are exempt from scheduling, irrespective of quantity.

A product containing 3% diclofenac (Solaraze®) is available as a S4 product for the management of actinic keratosis.

Quality Use of Medicines

Quality Use of Medicines (QUM) is one of the central objectives of Australia's National Medicines Policy[1]. [redacted] believes that QUM is best supported by the supply of medicines through a pharmacy with access to specialised professional support and advice from a pharmacist. As such, we oppose exempting medicines from scheduling because we are concerned that the proposed arrangements may facilitate use of the medicines in a manner that does not align with QUM principles. Access through the community pharmacy sector is extensive, with reasonable after-hours access and emergency access, often accompanied by additional services such as home delivery and monthly accounts.

There are no controls or quality assurance processes in place for the supply of medicines through the grocery channel and grocery customers can purchase one or one hundred packs of medicines exempt from scheduling without any question asked about the condition, the patient history or the use of the medicine.

Key Points

1. Confusion from listing different strengths under the one schedule of the SUSMP
2. Safety profile of NSAIDs warrants supply of stronger topical preparations to be managed through the pharmacy sector.

[redacted]

3. The inclusion of warnings and directions on packs does not surmount the issues associated with poor consumer health literacy without the opportunity for counselling.

Comments

[redacted] has considered the scheduling and exemptions proposal for topical diclofenac preparations with particular reference to the following subsections of the *Therapeutic Goods Act 1989 – Section 52E (1)*:

(a) the risks and benefits of the use of a substance

- All NSAIDs have a similar capacity to cause renal impairment, congestive heart failure, hypertension and oedema.[2]
- NSAIDs are associated with significant cardiovascular risks, with ibuprofen associated with the highest risk of stroke, followed by diclofenac, and diclofenac associated with the highest risk of cardiovascular death.[3]
- Chronic sustained systemic exposure to NSAIDs, particularly in patients over 65 years of age is of concern owing to documented increased risk of gastrointestinal and cardiovascular events.[4]
- While evidence based reviews show 1% topical diclofenac to be an effective and well tolerated treatment in painful and inflammatory conditions for short-term use, further research is recommended. [5]
- There is systemic exposure to diclofenac following normal use of Voltaren® gel (1% diclofenac), up to 6% of the systemic levels of a single oral dose of diclofenac sodium. Concomitant administration of diclofenac gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.[6]
- Stronger topical preparations will cause greater systemic exposure, even with proper use. Inappropriate use such as greater frequency or larger areas of application risk even greater systemic exposure.

  With the unrestricted availability of aspirin and ibuprofen, there is a potential for people to combine these with topical diclofenac use, increasing the risk of systemic adverse effects. The elderly will be particularly at risk and considering the incidence of osteoarthritis in this age group, there is a strong likelihood that they may use topical NSAID preparations as well as oral NSAIDs; particularly with targeted marketing campaigns.

(b) the purposes for which a substance is to be used and the extent of use of a substance

- As an anti-inflammatory, the recommended dosage for 1% topical diclofenac is[7]:
  - 2g per joint per application for upper extremities (hand, elbow, wrist), with a maximum of 4 applications (8g) per joint per day
  - 4g per joint per joint per application for lower extremities (foot, ankle, knee), with a maximum of 4 applications (16g) per joint per day
  - a total maximum of 32g of gel per day.

- With this dosage in mind, we assume that a 2% gel would equate to a total maximum of 16g of gel per day and a 4% gel would equate to a total maximum use of 8g per day. Considering the risks described under section (a), it would be

[redacted]

essential for consumers to be supported in the appropriate use of stronger preparations.

[redacted] suggests that ideally this would be through discussion with a pharmacist as a S3 medicine. Alternatively, with appropriate training of pharmacy assistants, stronger products could be included in S2 to facilitate referral to a pharmacist as appropriate.

(c) the dosage, formulation, labelling, packaging and presentation of a substance

- Applying restrictions to different strengths of a medicine under one schedule of the SUSMP can be confusing for pharmacists. Under the proposal, diclofenac for dermal use could be listed as a S4 medicine if:
    - in preparations containing more than 4% when not indicated for solar keratosis
    - in preparations indicated for solar keratosis.

[redacted] is concerned that pharmacists may be confused as to when they can or cannot supply stronger topical diclofenac preparations without a prescription. As an example, could the S4 product Solaraze® (diclofenac 3%) be supplied without a prescription as an anti-inflammatory? If so, how can it be supplied so that pharmacists do not breach either national or jurisdictional legislation. [redacted] understands that merely applying a dispensing label with directions does not meet regulatory requirements.

This is already an issue with mometasone nasal spray. Although mometasone is included in S2 of the SUSMP for nasal sprays for the treatment of allergic rhinitis in adults and children 12 years of age and over, the only available product on the market, Nasonex®, is a S4 product. [redacted] is regularly contacted by pharmacists enquiring if Nasonex® can be supplied without a prescription. Our advice has been that as Nasonex® does not meet the labelling and packaging requirements for an S2 medicine, it should not be supplied as such without advice from jurisdictional pharmacy services. Feedback from pharmacists indicates that advice from jurisdictional pharmacy services has not necessarily clarified the matter and pharmacists remain confused on this issue.

We are concerned that the proposed listing for diclofenac could cause similar confusion. Currently, irrespective of whether Solaraze® is indicated for solar keratosis, as a 3% topical product it remains S4. As such, we suggest that limiting the S4 entry by strength rather than indication provides greater clarity and we would support an S4 entry for diclofenac in preparations for dermal use containing 3% or more of diclofenac.

- Regarding the proposals to exempt topical diclofenac preparations containing 2% or less, or 4% or less diclofenac, [redacted] is concerned that product labelling will not adequately ameliorate safety risks. Australian Bureau of Statistics (ABS) have identified[8]:
    - 46% of Australians aged 15 to 74 years as not having sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60% attained scores below the minimum requirement to meet everyday needs

[redacted]

- only 36% and 38% of people whose language was not english attained scores at or above the level that demonstrated sufficient prose and document literacy respectively to meet everyday needs.

[redacted] is concerned that topical diclofenac products may be inadvertently misued by people who do not understand the directions or the precautions. There would be a risk of administration to children or the elderly, or use for extended periods or in combination with other NSAIDs (including oral dosage forms) without consulting a health professional. This is particularly problematic as there is currently no quantitative limitation to exemptions for the 1% topical diclofenac and the risk would be increased with exemptions applying to stronger preparations.

In the interest of public safety, it is essential that support is aimed at the lowest common denominator. For people with limited health literacy such as those from culturally and linguistically diverse (CALD) or lower socio-economic backgrounds or who are poorly educated, relying solely on having information on a medicine pack is not appropriate if there is any risk of misuse.

(d) other matters in public health interest

- [redacted] the National Coordinating Committee on Therapeutic Goods (NCCTG) with an annual report on the outcomes from the Standards Maintenance Assessment (SMA) Program (previously known as the Mystery Shopper Program), conducted as part of the Quality Care Pharmacy Program (QCPP).

  The most recent SMA results indicate a trend for improvement in SMA scores and almost all consumers receiving some advice from pharmacy personnel with the purchase of S2 or S3 medicines. It would be expected that there would be no information gathering or provision of professional advice associated with medicines supplied through the grocery sector.

  It is also worth noting that pharmacy assistants must complete appropriate training regarding S2 and S3 medicines as part of QCPP accreditation and that since April 2010, refresher training for pharmacy assistants, focused on applying S2/S3 professional supply protocols, has been needed for QCPP re-accreditation.

Conclusion

Topical diclofenac is a useful and relatively safe treatment for pain and inflammation when used appropriately. However, diclofenac and other commonly available NSAIDs are associated with increased cardiovascular risks. Even with the use of topical preparations, these risks are increased with stronger products, inappropriate use such as more frequent application or application to larger areas, or concomitant use with oral NSAIDs or aspirin.

Stronger products should be included in S4 of the SUSMP, providing clarity to pharmacists and prescribers and moderate strength topical diclofenac products could be available without the need for a prescription with access to advice from a pharmacist.

[redacted]

[redacted] therefore considers the appropriate scheduling of diclofenac for dermal use to be:

- S4 for preparations containing 3% or more diclofenac, irrespective of indication
- S3 for preparations containing more than 1% and less than 3% diclofenac.

[redacted] would also support S2 for topical preparations containing more than 1% and less than 3% diclofenac on the condition there was a commitment from sponsors to support pharmacy assistant training.

Reference Sources:

[1] http://www health.gov.au/internet/main/publishing nsf/Content/National+Medicines+Policy-1
[2] NPS RADAR August 2005; Elevenated cardiovascular risk with NSAIDs
[3] S Trelle, S Reichenbach, S Wandel et al; Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis; BMJ 2011; 342:c7086 doi:10.1136/bmj.c7086
[4] Safety of diclofenac topical solution compared with oral diclofenac for treatment of osteoarthritis of the knee in patients aged ≥65 years; 30th Annual Scientific Meeting of the American Pain Society; 19 May 2011
[5] J.Zacher, R.Altman, N.Bellamy et al; Topical diclofenac and its role in pain and inflammation: an evidence-based review; Current medical research and opinion; 2008; Vol 24, No 4; pp 925-950
[6] Voltaren gel Prescribing Information; September 2009; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047 htm
[7] S.Haroutiunian, DA Drennan & AG Lipman; Topical NSAID Therapy for Musculoskeletal pain; Pain medicine Vol 11, Issue 4 pp 535-549; April 2010
[8] ABS 4228.0 – Adult Literacy and life Skills Survey, Summary Results, Australia, 2006 (Reissue); www.abs.org.au

[redacted]

[redacted]

7 September 2011

[redacted] to the Advisory Committee for Medicines Scheduling – Meeting of 19 October 2011

Proposal

2.4 Famciclovir – seeking advice on a proposal to reschedule 1500mg or less of famciclovir from Schedule 4 to Schedule 3 when in oral preparations for the single dose treatment of herpes labialis (cold sores) in immunocompetent patients.

[redacted] supports the proposal for including famciclovir in Schedule 3 for packs containing up to 1500mg famciclovir, supported by professional protocols for pharmacists developed by the profession.

[redacted]

[redacted]

Background

Herpes Simplex Virus type 1 (HSV-1) causes recurrent herpes labialis (cold sores), a common disease afflicting up to 40% of adults worldwide . Approximately 90% of recurrent HSV-1 infections manifest as non-genital disease, primarily as orofacial lesions.

After initial infection with HSV-1, the virus may be reactivated by physical trauma, stress, illness, sunlight or other unknown factors and produce painful vesicular lesions. Recurrent infections last around 5-7 days and then clear spontaneously. Individual herpetic lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring.

Famciclovir is a pro-drug for the active metabolite penciclovir, used to treat HSV-1 (and HSV-2). In January 2007, oral famciclovir was approved by the Therapeutic Goods Administration (TGA) for the treatment of recurrent herpes labialis in immunocompetent patients.

Famciclovir is currently listed as a Schedule 4 (S4) medicine in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Aciclovir 5% cream is the standard topical therapy used to treat herpes labialis applied to the affected area five times a day at four hourly intervals for 5-7 days. Aciclovir cream is not scheduled and is registered for the treatment of herpes labialis.

At its meeting of November 2009, Medsafe in New Zealand agreed to reclassify oral famciclovir from a prescription medicine to a pharmacist-only medicine[1].

Key Points

1. The use of famciclovir for the treatment of cold sores can be effectively managed through the pharmacy sector without the need for a prescription.
2. The need to commence cold sore treatments as soon as possible would be addressed by a S3 listing for famciclovir, providing prompt access to an effective and safe cold sore treatment.
3. Pharmacists are experienced in triaging patients and referring for further medical support when required. The availability of professional support materials for pharmacists would assist in maintaining and improving this competency.

Comments

[redacted] has considered the proposal to reschedule famciclovir with particular reference to the following subsections of the *Therapeutic Goods Act 1989 – Section 52E (1)*:

(a) the risks and benefits of the use of a substance

- Studies have demonstrated that a one day 1500mg course of famciclovir decreases the mean healing time for cold sores by about two days.[2] Patients with ulcerative cold sore lesions treated with famciclovir reported a 29-36% reduction in lesion healing

[redacted]

time, however, distributing antiviral agents to the site of viral replication as early as possible is important.[3]

- The results from penciclovir and famciclovir patient studies showed no resistance occurred as a result of treatment with either famciclovir or penciclovir[4].
- Caution is required when recommending famciclovir for people with reduced renal function. There are also many other products available without prescription for which caution exists in renal impairment. As an example, a search of the Full Product Information available from MIMs Online for the following products indicated the following precautions:

    - Paracetamol (Panamax) – caution with hepatic or renal dysfunction
    - Ibuprofen (Nurofen) – caution with severe hepatic, renal or heart failure
    - Pseudoephedrine (Sudafed) – caution with severe hepatic or renal dysfunction
    - Promethazine (Phenergan) – caution with renal failure or impairment.

  All of these products are currently available within pharmacy without prescription. Considering that the elimination of drugs is mostly through liver metabolism and/or kidney excretion, it would be expected that a review of most products would advise caution with reduced renal and/or liver function.

  Full Product Information for famciclovir (available from MIMs Online), recommends that dose adjustment in immunocompetent people is only needed if renal impairment is below 30ml/min/1.73m2 and in immunocompromised people, no dose adjustment is necessary unless renal impairment is below 50ml/min/1.73m2.

  [redacted] has confidence that supported by guidelines and training, reasonable triage by a pharmacist should negate this risk. If there is any uncertainty, pharmacists are trained and quite prepared to refer the patient to their doctor.

(b) the purposes for which a substance is to be used and the extent of use of a substance

- Treatment of cold sores should be initiated as early as possible. The availability of an oral treatment in Schedule 3 (S3) would increase patient access for earlier treatment. This would be particularly useful for patients who find topical aciclovir to be ineffective.
- Australia Bureau of Statistics (ABS) survey data show that 12% of Australians have indicated delays of more than 2 days to see a general practitioner (GP) for urgent care and 12% of people in outer regional or remote Australia visit hospital emergency departments because GP waiting times are too long.[5] The availability of famciclovir as a S3 product would resolve this issue for patients with cold sores, ensuring prompt access when needed.

(c) the toxicity of a substance

- There has been no clinically significant drug interactions reported with famciclovir or penciclovir and famciclovir is generally well tolerated with headache being the most common reported adverse effect when used to treat herpes labialis[3].

[redacted]

(d) the dosage, formulation, labelling, packaging and presentation of a substance

- Data from clinical studies confirm that short-course, high-dose oral antiviral therapy should be offered to patients with recurrent herpes labialis to accelerate healing, reduce pain and most likely increase treatment adherence.[6]
- Topical treatments do not appear to be as effective as systemic medications.
- The recommended dosage [of famciclovir] for recurrent herpes is 1500mg as a single dose or 750mg twice daily.[7] A once or twice daily dosage regimen with oral famciclovir is much easier to manage than a regimen requiring topical application five times a day.
- Topical application is likely to only be to blistered areas whereas systemic treatment provides much greater coverage.
- There is an increased risk of cross infection between the lips and other body parts (e.g. eyes) with the use of topical treatments for herpes labialis. This can be demonstrated by the fact that topical aciclovir treatments recommend care in application to prevent 'auto-nucleation of other body sites and transmission of infection to other persons'. This risk of cross-infection is significantly reduced with the use of oral treatment as there is less need to touch the lesion, particularly during viral shedding which occurs before and after appearance of the lesion.
- Although there may be a risk of off-label use, the cost of small pack sizes of a S3 product would be a disincentive as it would be far more cost-effective to obtain treatments intended for ongoing use that are subsidised on the Pharmaceutical Benefits Scheme (PBS).

(e) other matters in public health interest

- With appropriate support materials, pharmacists should be in a position to reasonably assess a person's immune status. Pharmacists already do this for other medicines that are available without prescription and which should not be initiated in immunocompromised individuals without medical review (e.g. anti-thrush products or topical aciclovir).
- In preliminary discussions, the sponsor has indicated to [redacted] that it would be interested in developing supporting professional materials for pharmacists to ensure competence in patient triage for the provision of a S3 famciclovir product. Ideally, these materials should be developed by the profession. [redacted] is willing to collaborate with other professional bodies and the sponsor in developing guidelines and/or training and protocols for pharmacists.
- Pharmacists would be in a position to assess whether patients were purchasing multiple packets (likely off-label use) or making repeat purchases too frequently (likely immune issue) and would be in a position to refer the patient to their doctor.
- If the decision to include famciclovir in Schedule 3 is supported, [redacted] suggests restrictions should be reconsidered for the proposed SUSMP entry. We believe limitations such as 'for immunocompetent patients' are better addressed by professional mechanisms such as protocols, that are consistent with the registered indications of the product.

[redacted]

Conclusion

[redacted] supports the inclusion of famciclovir in S3 of the SUSMP for packs containing up to 1500mg famciclovir. Acknowledging that products would be for the treatment of cold sores in immunocompetent people, we believe this is better managed through the registration process and supported by effective labelling and professional support materials for pharmacists.

Reference Sources:

[1] http://www.medsafe.govt.nz/profs/puarticles/medicines%20classification%20update.htm
[2] SA Pierre, BL Bartlett, BJ Schlosser; Practical Management Measures for Patients with Recurrent Herpes Labialis; Skin Therapy letter; Vol 14, No 8, Nov-Dec 2009
[3] J Harmenberg, B Oberg et al; Prevention of ulcerative lesions by episodic treatment of recurrent herpes labialis: a literature review; ACTA Derm Venereol 2010; 90: 122-130
[4] MIMS Full Prescribing Information – Famvir Tablets
[5] ABS 4839.0.55.001 - Health Services: Patient experiences in Australia 2009
[6] Gilbert S, Corey L, Cunningham A et al; An update on short-course intermittent and prevention therapies for herpes labilais; Herpes 2007 Jun; 14 Suppl 1:13A-18A
[7] RGH Pharmacy e-Bulletin Vol28(11): Jan 28,2008; Oral famciclovir for herpes labialis

[redacted]

[redacted]

Submission to
The Scheduling Expert Advisory Committee
October 2011 Meeting

Synthetic Cannabinoids

[redacted]

7 September 2011

Scheduling of Synthetic Cannabinoids

"While banning is the traditional approach to drugs classed as dangerous, a regulatory 'no-man's-land' exists around substances which do not clearly pose a "medium" level of risk. I know that harm minimisation has got a mixed press in some cases, but there's a lot to be said for trying to manage and contain the situation rather than almost a knee-jerk reaction of banning without the evidence to back that up." The Director of the Institute of Environmental Science and Research (ESR), Dr Keith Bedford *New Zealand Herald June 11 2011*

[redacted] supplying synthetic cannabinoid substances for a number of years without incident.

The Delegate requests that we limit our submission to the proposal and address matters mentioned in section 52E of the Therapeutic Goods Act. These are
a. The risks and benefits of the use of the substance
b. The purpose for which the a substance is to be used
c. The toxicity of a substance
d. The dosage formulation, labelling, packaging and presentation of a substance
e. The potential for abuse of a substance
f. Any other matters that the Secretary considers necessary to protect public health.

Synthetic Cannabinoids are game changers for legislators and for drug policy, in much the same way the internet was for media regulation and censorship. The analogues of cannabis currently being considered are the tip of the iceberg. Analogues of cocaine, morphine, kava and opium will be in the market place over the next few years. Governments have to understand that banning these products means they lose control of them.

a. The risks (including toxicity) and benefits of the use of the substance
Risks to public health are generally low as when these substances are presented as a herbal smoking blend the substances and have been highly diluted with inert herbal material. Reports of abusive use and adverse reactions have been highly publicised but in reality are extremely rare when you consider the overall number of users.

Toxicological effects of the cannabinoids appear to be minor, as few adverse health effects have been seen except in very heavy users. Anxiety and panic attacks are the

only side effects commonly reported from diluted smoking blends, and usually occur in inexperienced users who fail to follow dosage instructions or are not provide with information about usage.

In the majority of cases regulating the permitted concentrations of active ingredients and the way in which herbal smoking blends are sold would be a much more effective way of regulating the harms of these compounds than banning them outright.

As stated in the delegate's July 2011 report on these substances very little peer-reviewed research has been conducted on the therapeutic benefits. [redacted] have reported that a considerable number [redacted] have purchased these substances to deal with a number of health issues including pain relief, depression and to assist in reducing the shaking effects of Parkinson's disease.

The New Zealand Expert Advisory Committee on Drugs reported in their 11 November 2010 report (page 9) that there was some qualitative data that suggests that users of these substances find that they have a therapeutic value on a number of conditions including depression, anti nausea and pain relief.

There are a number of recent reports that have studied the therapeutic potential of cannabinoids particularly as an alternative to opioid drugs. These include:

The analgesic potential of cannabinoids. Elikkottil J, Gupta P, Gupta K. Journal of Opioid Management. 2009 Nov- Dec; 5(6): 341-57.

Interaction of the cannabinoid and opioid systems in the modulation of nociception. Welch SP. International Review of Psychiatry. 2009 Apr; 21.

The additive antinociceptive interaction between WIN 55,212-2, a cannabinoid agonist, and ketorolac. Ulugöl A, Ozyigit F, Yesilyurt O et al. Anesthesia and Analgesia. 2006 Feb

Antinociceptive synergy between the cannabinoid receptor agonist WIN 55,212-2 and bupivacaine in the rat formalin test. Kang S, Kim CH, Lee H et al Anesthesia and Analgesia. 2007 Mar

It is interesting to note that the relatively recent use of a variety of these substances in smoking blends has led to a resurgence of their use in research.

The other benefit that has been noted is that people are using it as a milder alternative to cannabis.

b. The purpose for which a substance is to be used

The majority of Australian who use these substances do so for recreational purposes and this appears to be the real reason that these substances are being called on to be prohibited or strictly scheduled. Scheduling and drug policy needs to recognize

this and not operate within a social vacuum. The Act does not appear to allow for a purely recreational substance to be scheduled so the lack of therapeutic value takes precedence.

While this submission is not the appropriate place to argue Australian drug policy, we do argue that these substances should be available and that prohibiting their use will cause more harm than good.

When these substances are available in a regulated and controlled manner, they will not cause death or dependence and would be far safer than many legal products available over the counter now.

In considering the scheduling of broad families or classes of these cannabinoids it should be noted that many of the compounds that would be caught in such a decision, have no current use.

As discussed in the delegate's report in July a large variety of synthetic cannabinoids exist, of which only a small proportion have been sold or could be potentially subject to abuse or even use. Most known cannabinomimetic drugs fall into one of several loosely defined families with related chemical structure and generally similar pharmacological effects, but within families, both potency and toxicity can vary markedly. To strictly schedule these broad families would mean that many absolutely harmless substances would be incorrectly scheduled. It could also stymie research and development of therapeutic uses for these substances.

c. The toxicity of a substance

"I think although there's an appalling lack of information on the risks and toxicity of these new substances, every indication seems to be that they are not a high or even medium level of risk - there's a low level of risk." *The Director of the ESR,* Dr Keith Bedford *New Zealand Herald June 11 2011*

In regards to toxicity, the substances being considered vary widely. [redacted] has noted that as a broad generalisation, the subjective effects of synthetic cannabinoids tend to correlate with their chemical structure, with compounds closer in structure to THC more accurately replicating the effects of actual cannabis. However the substantial differences in affinity and efficacy between different compounds in the same family mean the potency by weight and intensity and type of effects produced can change dramatically between different compounds, with only slight changes in structure. For instance JWH-073, the 1-butyl homologue of JWH-018, is some 3-5x weaker by weight and has a substantially lower "ceiling" on maximal effects, despite differing by only a single CH2 repeating unit in the length of the indole 1-alkyl side chain, while the 1-hexyl homologue JWH-019 is around 75% the potency of JWH-018 but with similarly weaker subjective effects.

Some weaker compounds such as WIN 55,212-2 appear to have substantially lower efficacy as partial agonists than THC, and produce only weak cannabinomimetic effects with a low ceiling on maximum activity and no further increase in effects

once this is reached, no matter how large a dose is taken. These are not useful for smoking blends, but may have other potential applications and in any case can safely be considered to be of low risk of harm.

The synthetic cannabinoids have a very low potential to cause death in most cases. Large overdoses of JWH-018 powder have produced effects such as panic attacks, vomiting, sudden loss of consciousness and even convulsions, which have not been seen with other related compounds. To date we are not aware of a death caused by these substances.

The synthetic cannabinoids are in most cases unable to induce physical or psychological dependence comparable to that of cannabis, aside from some specified compounds such as JWH-018, (C8)-CP 47,497 and HU-210 which may produce physical or psychological dependence similar to or greater than that of cannabis following prolonged heavy undiluted use.

d. The dosage formulation, labelling, packaging and presentation of a substance

[redacted] believe that regulation in this area is crucial and will be the most effective regulatory avenue to reduce harm. These substances should only be available to adults. The advertising or promotion of them should be strictly limited but consumer information about what they are buying is crucial particularly in regards to dosage and ingredients.

These controls could include:

- A minimum purchase age of 18 years
- Restrictions limiting all advertising (except internet-based advertising) to only the inside of a premises selling restricted substances and a requirement that such advertising not be visible or audible from outside such premises.
- Prohibitions on selling such products from any venue with a liquor license, or from service stations, or from non-fixed premises such as caravans or street carts
- Restrictions on where these substances can be sold ensuring that they are only sold in age restricted venues
- Requirements for all products to contain warning labels, including warning against driving or operating machinery following use, and contact details of the manufacturer and the National Poisons Centre
- Requirements for all products to clearly state the synthetic cannabinomimetic substances they contain on the packet and the recommended dosage

Dosage
Manufacturers and their chemists have recommended the following dosages as an example;
herbal smoking blends mixed, sprayed or infused with (C8)-CP 47,497 at a maximum concentration of 50 milligrams of drug per gram of herbal smoking blend

Herbal smoking blends mixed, sprayed or infused with JWH-073, JWH-019 or JWH-081 at a maximum concentration of 100 milligrams of drug per gram of herbal smoking blend

Herbal smoking blends mixed, sprayed or infused with JWH-250 or 1-pentyl-3-(4-methoxynaphthoyl) indole at a maximum concentration of 150 milligrams of drug per gram of herbal smoking blend

This could be monitored relatively easily in much the same way as TGA officers are currently monitoring "herbal" aphrodisiac products to ensure that they do not contain any prescription drugs for erectile dysfunction.

e. The potential for abuse of a substance
There have been a number of media reports of abuse and misuse but no actual research.

Reports of abusive use and adverse reactions are highly publicised by the media but in reality are extremely rare compared to the overall number of users, and tend to be restricted to use of either pure powder forms of the drugs, or smoking blends containing high concentrations of the strongest synthetic cannabinoids such as JWH-018.

It is very rare for consumers to take large enough doses to cause significant side effects aside from anxiety, though panic attacks have been reported in susceptible individuals following even fairly small diluted doses. Recent media reports have also configured strong coffee as causing these problems. [redacted] believes that regulations on the strength of blends and the way in which they can be sold as detailed previously would greatly reduce the frequency and severity of these already rare adverse reactions.

Recommendations and Other Matters

1. These substances should not be scheduled as complete families to avoid completely harmless substances being incorrectly scheduled.

2. Some compounds are of sufficiently low risk of harm or low concentration that no scheduling is required. This will in general be restricted to CB2 selective compounds such as JWH-015 and JWH-133. Many cannabinoid receptor ligands will not need regulation however due to their lack of cannabinomimetic psychoactive effects, and efforts should be made to avoid placing these under control as this could hinder scientific and medical research, but would fail to achieve any useful aims.

3. Some substances should be restricted but the majority should be included in Schedule 5 or Schedule 6 with strict controls on dosage, information and availability

4. Some of the cannabinomimetic compounds that have become subject to human use, are however, unquestionably of moderate risk of harming, to an extent which is difficult to minimise through dilution into standardized commercial products or encouraging safer routes of administration. These compounds should remain or be placed into Schedule 9.

    - JWH-018, due to issues with toxicity and abuse potential. This compound has proved unusually problematic and has a particular tendency to cause anxiety and serious adverse reactions, even when diluted in smoking blends
    - HU-210, as it is very potent and has severe side effects and a very long duration of action.
    - AM-694, as many toxicity concerns have been raised about its chemical makeup

5. Regulations under schedule 6 should be used to encourage use of a restricted subset of compounds with relatively lower risks, and limit amounts that can be used and dosage forms they are used in. Pure powder forms of the cannabinomimetic drugs should be prohibited from public sale.

6. Exemption for importation and resale of bulk forms of the drug so that approved dosage forms can be manufactured and packaged domestically is required. An exemption for individual importation for personal use could also be permitted but only in very small quantities (e.g. 1 gram or less).

7. Regulations must be introduced to enforce the display of health warnings and accurate and complete lists of ingredients on packaging, as well as regulate advertising and marketing practices to prohibit marketing to young people or other vulnerable populations.

8. Recommended maximum dosage limits for specified dosage to include;
    - "Herbal smoking blends" mixed, sprayed or infused with (C8)-CP 47,497 at a maximum concentration of 50 milligrams of drug per gram of herbal smoking blend

    - "Herbal smoking blends" mixed, sprayed or infused with JWH-073, JWH-019 or JWH-081 at a maximum concentration of 100 milligrams of drug per gram of herbal smoking blend

    - "Herbal smoking blends" mixed, sprayed or infused with JWH-250 or 1-pentyl- 3-(4-methoxynaphthoyl) indole at a maximum concentration of 150 milligrams of drug per gram of herbal smoking blend

In other countries where certain cannabinoids have been effectively prohibited, other compounds come onto the market. We have already seen this in Australia. A far more effective control would be to restrict the concentrations and where and how they are sold and who they are sold to. If a strong regulatory framework is put around those chemicals at the lower end of the scale, it is hard to see the black market achieving any further toehold on this genre of substances than they currently have. However if all cannabinoid smoking mixes are completely banned, it makes sense that the black market will simply ad this genre to their current list of contraband.

Imposing restrictions and regulatory requirements on the synthetic cannabinomimetic substances and the permitted ingredients of 'herbal smoking blends', could be fairly easily carried out using the processes set out in existing scheduling legislation. States could also take advantage of their existing legislation on Non Tobacco Smoking substances.

With the synthetic cannabinomimetics particularly, there is a great risk of encouraging the use by the public of new and potentially more dangerous substitutes in response to placement of certain compounds into the controlled substances schedules.

Finally we would caution against any attempts to introduce 'broad' scheduling of synthetic cannabinomimetics that could have unintended consequences on other products. In the US, eight states inadvertently banned Tylenol, chocolate sauces and even some motor oil additives in their haste to proclaim their 'tough on drugs' stance to the community. The political fallout from this sort of 'catch-all' approach is one thing but the community expectations around drug policy are not that it should be so wide as to prohibit commonly used goods or to prohibit future commonly used goods.

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

5th September, 2011

Dear Sir/Madam,

Advisory Committee on Medicines Scheduling: 2.9 Synthetic Cannabinoids

I am responding to the invitation for public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 published on 10th August 2011 for ACMS and ACCS October meetings.

[redacted]The ever expanding number of plant cannabinoids, psychoactive cannabinoid metabolites, endogenous cannabinoids, classical cannabinoids, synthetic cannabinoid receptor agonists, allosteric modulators of cannabinoid receptors, and endocannabinoid activity enhancers are also attractive to users of herbal cannabis who primarily seek the effects of delta-9-THC and appear to share similar harms.

The evidence base on synthetic cannabis related harms is scant at this early stage. A published series of case history reports on JWH-018's potential to precipitate psychosis in vulnerable individuals.[1] A recent internet survey of "Spice" in the first two months of this year from 13 countries and 42 states of the USA[2] found that while most users did so out of curiosity and because they liked the effects, 40% of the sample had negative or unwanted effects. Almost one third reported using synthetic cannabinoids to get intoxicated while avoiding detection in drug urinalysis testing in workplace or criminal justice settings. The same study also noted that these products (along with whatever herbal products it is prepared with) are smoked.

Given that there are no pharmacotherapies available for the management of cannabis withdrawal or dependence it would be preferable for these substances to be in Schedule 8 rather than 9 so that they can be used in appropriately conducted clinical trials. [redacted] This preparation contains plant cannabinoids, but in future some synthetic cannabinoids may be useful for this condition (in addition to analgesic and other actions) and these should be available for research purposes. The dibenzopyrans, Dronabinol and Nabilone, have also shown promise for the management of cannabis dependence in addition to their use in the management of nausea and as an adjunct analgesic.

[redacted]

[redacted]

The current list of 8 classes of synthetic Cannabinoids is quite comprehensive although not complete (missing JWH-171, JWH-176 and JHW-030 for instance) but the science will always be ahead of the policy in such matters.

For this reason I recommend that the and/or option be adopted. It should be noted that the term cannabinomimetic is also used to describe preparations of *Echinacea Purpurea* and *Spilanthes Acmella* that are said to have a high affinity for CB1 and CB2 receptors and are reportedly used by body builders to stimulate appetite. Use of clause two alone would also be problematic. Demonstration of the pharmacodynamics and pharmacokinetics of any product suspected of being a synthetic cannabinoid, will be challenging. I am not a lawyer but if it is possible, the onus of proof should perhaps be on the individual wishing to possess or sell the preparation that is suspected of being cannabis-like, rather than the Commonwealth. The use of both clauses should reduce enforcement challenges.

In summary, as a scientist interested in the management of cannabis dependence I would advocate that synthetic cannabinoids be included in Schedule 8 to allow their testing in high quality clinical trials given the developing evidence base of their possible application in this and other disorders.

Yours faithfully,

[redacted]

1. Every-Palmer (2011). Synthetic cannabinoid JWH-018 and psychosis: an explorative study. *Drug and Alcohol Dependence, 117,* 152-157.
2. Vandrey, R., Dunn, K.E., Fry, J.A. & Girling, E.R. (in press). A survey study to characterize use of Spice products (synthetic Cannabinoids). *Drug and Alcohol Dependence, available on line 10th August 2011*

[redacted]

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Re: Notice inviting public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990

Thank you for the opportunity to provide comment on the proposed amendments to the Poisons Standard under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990, to be discussed at the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling ACCS meetings being held in October 2011. [redacted]

In a global environment where increasingly there are calls to change the approach of governments from a criminal justice and law enforcement focus to more humane and effective ways to reduce the harm caused by drugs, some Australian governments have been quick to ban synthetic cannabinoids in response to presentations at hospital emergency departments. After consuming these synthetic cannabinoids such as 'Kronic', there have been reported cases of people suffering from symptoms such as heart palpitations, hallucinations and paranoia. These experiences are indeed worrying and suggest that care needs to be taken in their use and that comprehensive research into the effects on short term and long term health is required. Little is known about these at this stage, especially in relation to possible side effects, adverse reactions, potential for dependence, and other effects on humans.

There are of course a number of risks associated with the use of such substances, which impact on the possible health effects mentioned above. These include potency of the product used, half life of the psychoactive substance (a long half life has the potential to induce a prolonged psychoactive effect), their interaction with other substances, and variability in the product smoked with respect to the type of substance present and the concentration of the synthetic cannabinoid. The risk of overdose increases as the concentration of the active ingredient increases but unfortunately the packaging does not indicate the strength of the synthetic

[redacted]

cannabinoid. Generally, products sold have had little information on any of the ingredients and therefore users have been unable to identify potential risks.

Many would argue that the most effective way of limiting any potential harm caused by the use of synthetic cannabis is to regulate its use. The blunt instrument of banning a product only serves to encourage producers to find other chemicals that will produce a similar effect, and encourage a black market that leaves the use of these types of products uncontrolled. As a result, a situation is created where you achieve the opposite of what had been intended, with the risk of harm *increasing* rather than decreasing. The regulation of synthetic cannabinoids would allow activities such as standardisation of the product, licensing requirements, age restrictions, restrictions over advertising and appropriate labeling to identify the concentration of the active ingredient/s and other substances in the product. These strategies would help to reduce the risk to consumers.

Synthetic cannabinoids may in fact have potential benefits which if regulated could, for example, make life more comfortable for those experiencing significant health problems such as those associated with cancer and severe pain. [redacted] is aware that some research work is being undertaken to understand the potential benefits of these products and therefore recommends that any scheduling of synthetic cannabinoids allows for their use in such research.

Thank you again for the opportunity to provide comment. [redacted]

[redacted]

To: The Medical Advisory Committee.

Hello [redacted] and I would like to put forward my opinion on the forthcoming amendments to the Drug Act,

I am concerned about the submission to the amendment of the drug act (2.9) to include Synthetic Cannabinoids into the schedule 9 or 8 of the drug act. I believe if any Cannabinoids are included in such schedule; this decision will effectively remove all Cannabinoids from research on the potential anti-Cancer properties, Alzheimer disease benefit, MS sufferer's spasm reduction, cancer cell Anti-Proliferators research, Etc. (1)

These are just a few of the benefits of these Cannabinoids to Australian researchers looking for the next wonder drug. This research is currently being done overseas and we need to encourage research here in Australia, not hinder it. Once included as a schedule 9 the red tape required for medical research makes it become unachievable to willing laboratories. The cannabinols are the great drug for cancer treatment of the future, some already available in the USA, UK and Australia on medical grounds for effect of treatment or pain suppression. We are just discovering of our Endo-cannabinol system and the benefits of cannabis and Cannabinoids to our health.

So I put to the committee,

Alcohol and Tobacco are Killing 100,000's people each year and harming many more, I am sure the ChemCentre and Drugs and Alcohol Office here in WA who together with the WA Police and the Department of Health who proposed the banning of Cannabinoids here in WA as well as all Australian research centres, already have the research and evidence applying to the "sufficient evidence of HARM" factor to have Alcohol and Tobacco listed on the schedule 9 part of the act. Surely these are more of primary concern to the greater health of the public than Cannabinoids?

Why artificial Cannabinoids and Cannabis are are deemed more damaging and dangerous and addictive, than Alcohol and Tobacco and coffee which are rated way more addictive and damaging and dangerous to oneself and others than Cannabis? (2)

By maintaining Cannabis as a schedule 9 you are pushing hard working taxpayers into becoming criminals because they are choosing to ingest a harmless to others, potential anti-cancernogens substance that is 100% natural and has 10,000 years of human trial, by forcing them to associate with criminals and break the law. Why maintain this?

Why is it that under labour and their decriminalisation laws in WA affecting Cannabis, the rate of use of cannabis fell (3) and I quote from National Drug Research Institute senior researcher Steve Allsop “Historically WA has had higher rates of cannabis use, and we're not really sure why that is, and while we should be concerned about these latest results that has to be tempered with the fact that generally there has been a downward trend since the late 1990s,” and that world research from USA, UK, Netherlands and Germany shown rate of use did not change when Cannabis was illegal compared to when under decimalisation(4). Why you think it best to maintain it on the schedule 9 and consider the evaluation done and recommendations on the cannabis laws when it was decriminalised (5)

Why ban water pipes? Although I don’t condone smoking Cannabis there is current research on the benefits of water filtration, and in all honesty you don’t have to be a rocket scientist to realise that by bubbling any smoke, regardless of the type, tobacco, Cannabis, Herbs etc through water removes numerous cancernogens and many other harmful substances you just have to look at it before and after, so in the interest of harm reduction and duty of care, please recommend this ridiculous law is removed from the act (6).

Ask yourselves why are patients even possibly some of your kin certainly mine, are sent home or placed in palliative care and condemned to die of disease like lung cancer by the medical fraternity when they can no longer help them but they are not offered information on the benefits of artificial Cannabinols and cannabis, examples like lung cancer patients and the Lewis lung adenocarcinoma research done in 1975 by A.E. Munson, L.S. Harris, M.A. Friedman, W.L. Dewey, and R.A. Carchman. (7) Surely when all else fail these poor souls deserve the right to try alternatives without the added concern and stress of facing the law.

Why is it that 1 in 2 Australians will be diagnosed with cancer by the age of 85? Yet Australia restricts the study and use of the most effective drug in Cannabinoids to fight cancer on our planet and have it scheduled 9 listed?

Why is it that since the artificial cannabinoid and herbal smoke became popular in WA the drug labs and growing dens all had lost customers, this is from personaly talking to many store owners of smoking retail outlets who all report their buyers have all gone back to pot smoking 300 in one store alone multiply that by the outlets and we are talking huge numbers Australia wide, is the decision to include artificial Cannabinoids and cannabis in the schedule 9 and not to tackle the real issue of Alcohol and tobacco really just supporting the organised drug gangs and the huge drug and oil corporations and isn’t this proof of this fact?

Consider the section of proposed inclusion to schedule 9 of the Act covering 'substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols'. This is a sketchy law to implement and worded terribly, the word “similar” is to broad for instance and to use tobacco and Alcohol as an example again, if you give a young teenager a cigarette or a cigar or a full glass of Alcohol and it’s the first time they have smoked or drank and never done any other drugs then surely after smoking or drinking the cigarette or alcohol they will have “similar” effects to Cannabinoids including tetrahhydrocannabinol?

If this amendment is included in the act then an arrest of an individual will depend on the police officers definition and interpretation of the words “effect and similar to” but we also need to consider and remember that the police are not actually medically trained to recognize the correct similarities of Cannabis and other substances as the effect changes substantially by the quality and strain and that some Cannabinoids are not able to be tested for. To base an arrest on observation and opinion rather than actual effects that can only be assessed under medical controlled conditions, is wrong and open to abuse the same goes for effects from nutmeg nuts grated and smoked, and lions tail plus thousand of other herbs and plants found in the garden for example, cacti that all contain mescaline or the Acacia tree containing DMT.

The inclusion of this clause and any similar umbrella clause could be interpreted as illegal as it is does not stipulate exactly what is illegal and what the clause is actually directed at. Australians have a right to know what is and what is not illegal before the police and courts could theoretically imprison us and under the current law and proposed inclusions and amendments to the Drug Act it is possible for someone in WA to be arrested for ingesting peppers or poppy seeds or nutmeg.

The laws in WA and Australia need to be uniform and our premiers should not have the right to enforce amendments without due course and being fully advised by the Australian Medical Advisory Committee and recognizing their decision first before local political influences.

The suggestion to include all Cannabinoids into the schedule 9 needs to be thoroughly investigated before acting so that the committee understands all the benefits of Cannabinoids of all types and are also included in your considerations. Please consider that the artificial Cannabinoids did reduce cannabis use and therefore substantially affected the profits from organised crime.

The decision to include or remove drugs into a schedule 9, such as Cannabinoids, where it then becomes a criminal offence to possess or grow a quantity for personal use, must be made with an companionate perspective with educated on cancer sufferers and Cannabinoids and recent addiction facts and statistics to form non bias, non opinionated recommendations from a committee that is able to recommend sound amendments and criminalising a herb like cannabis is not a sound one.

Realising that the Cannabis concerns of our society are health and medical problems not criminal justice systems issues is the first step in understanding why Cannabinoids need to be removed from the schedule 9. Personal use of Cannabinoids and cannabis should be separated from the organised crime aspect of cannabis the dealing and supplying should continue to be dealt with severely. We treat Alcohol addiction and Alcoholics with medical aid and support and not the criminal justice system because we realise this is a health and medical issue and cannabis is no different it must be treated similarly if we want to help people and minimise harm to the society and control what our kids ingest.

Pushing any product into the hands of the underground means any kid at any age can get access to it, drug dealers don't ask for ID, licence premises do. Drug dealers often contaminate their product in order to increase its weight or effect, controlled sale and distribution will ensure conformity to Australian codes written for such substance use. Some drug dealers fail to flush their Cannabis correctly before harvest or use fly sprays for bug infestation on the plants, this produces cannabis that is contaminated with poisonous chemical fertilizers and pesticides known to cause serious health effects, getting rid of or severely reducing the profit of these dealers by decimalisation must relate to people obtaining cleaner smoke.

Please also consider adding a clause in the amendment stating that Cannabis use, possession and the growing of two plants and either ingested by eating or by a vaporiser will be regarded as unscheduled in the drug act for personal use and decriminalised, as this is the best of worlds, health and medical.

Please consider these questions carefully and do your own research don't just rely on advisors please when amending the act, as concerned parents and citizens we have a right to question the government and its department's decisions and as your member of parliament is working for the people of Australia, they are obligated to ensure your decisions are justifiable and for the good of all Australians and are based of factual information.

Thank you

[redacted]

References

(1) https://www.greenpassion.org/index.php?/topic/26942-grannys-mmj-list-january-2011/

(2) http://www.procon.org/view.background-resource.php?resourceID=1492

(3) http://au.news.yahoo.com/thewest/a/-/latest/9919277/one-in-seven-high-on-cannabis/

(4) http://www.parl.gc.ca/Content/SEN/Committee/371/ille/presentation/korf-e.htm

(5) http://www.ndlerf.gov.au/pub/Cannabis_WA.pdf

(6) http://www.ukcia.org/research/EffectsOfWaterFiltrationOnMarijuanaSmoke.php

(7) http://www.ukcia.org/research/AntineoplasticActivityOfCannabinoids/index.php

[redacted]

7 September 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling

– Meeting of 19 October 2011

Proposal

2.9 Synthetic cannabinoids – seeking advice on the appropriate scheduling of synthetic cannabinoids and classes of synthetic cannabinoids, in particular inclusion in Schedule 8 or 9 with the possibility of cut-offs to unscheduled for lower concentrations.

[redacted] supports including synthetic cannabinoids in Schedule 8 if appropriate therapeutic indications exist, otherwise in Schedule 9. We question the need for exemption from scheduling for lower concentrations.

[redacted]

[redacted]

Background

Recently, synthetic cannabinoids have been legally marketed in Australia in cigarette form as 'Kronic Herbal Highs'[1], available for purchase through online vendors.[2]

Comments

Without participating in the debate regarding the legalisation of cannabis, [redacted] is concerned about the irresponsible use of synthetic cannabinoids obtained in the form of 'Kronic'. We believe the abuse potential warrants including synthetic cannabinoids in either Schedule 8 or 9 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

We suggest that if the consultation demonstrates a therapeutic need for synthetic cannabinoids, then both schedule 8 and Schedule 9 would be appropriate, with the Schedule 9 entry providing an exemption when separately specified in other schedules of the SUSMP. The proposed wording would suit a Schedule 9 entry, covering the class of synthetic cannabinoids. Individual molecules could be listed in Schedule 8 if appropriate.

We note that as part of the consultation, consideration is given to possible exemptions to scheduling for lower concentrations. We are concerned that such an approach may set precedence for exempting other drugs from scheduling in lower concentrations. We believe that the abuse/misuse potential associated with cannabinoids does not warrant any scheduling exemption and we would be interested in understanding the reasons behind such consideration. If greater access is required for legitimate therapeutic purposes, consideration should be given to inclusion within Schedule 2, 3 or 4.

We are also concerned that at a time when there is a decline in people who are smoking, the marketing of this substance in a cigarette format can have a detrimental effect on smoking cessation outcomes. We are also concerned with the marketing of these products as 'safe and legal alternatives to harmful illicit drugs'[3], particularly when the online safety section advises 'Keep hydrated. Party pills increase your heart rate and blood pressure so you will dehydrate faster especially when you are dancing. Do not take party pills at night if you intend to sleep in the next 6 hours.'

Conclusion

On face value, [redacted] supports including synthetic cannabinoids in Schedule 9, with an exemption if listed separately in other schedules of the SUSMP, particularly Schedule 8. We do not support an exemption from scheduling under any circumstances and believe that if greater access is needed, inclusion in another schedule would be more appropriate.

Reference Sources:

[1] http://www.kronic-in-australia.com.au/
[2] http://www.kronic-australia.com.au/
[3] http://www.infinitypartypills.com/Australia(1851698).htm

[redacted]

Public Submission Regarding Proposed Amendments to the SUSMP: adding Synthetic Cannabinomimetics to Schedule 8 or 9

Introduction

The TGA advisory committee recently propsed to schedule all cannabinomimetics, in either Schedule 8 or 9. I suggest that although it is necessary to regulate these substances, neither of these schedules are appropriate. Rather, the most appropriate approach would be to adopt a new Schedule that deals specifically with *inebrients*, where low-risk inebriants that have no therapeutic value, are restricted to over-18 sale, and quality control tests are performed. Whereas banning JWH will result in its becoming a black-market product, with a greatly increased potential for misuse and harmful effects, regulating JWH will impose safe boundaries on its use for both recreational and therapeutic reasons.

The Legislation

Under s52E Secretary to take certain matters into account when scheduling a substance:

(f) the risks and benefits of the use of a substance;
(b) the purposes for which a substance is to be used and the extent of use of a substance;
(c) the toxicity of a substance;
(d) the dosage, formulation, labelling, packaging and presentation of a substance;
(e) the potential for abuse of a substance;
(f) any other matters that the Secretary considers necessary to protect public health.

Use And Safety

As many of these categories overlap, I will address (a), (b) and (c) together.

Little study has been done on synthetic cannabinomimetics or their safety, and I recommend that more extensive scientific tests be performed on them. Nonetheless, a few studies on rats, as well as a large amount of anecdotal evidence on internet forums, do give us a good indication of their safety. When used appropriately and in their unadulterated form (eg, not containing pharmaceuticals as recently happened with the brand 'Kronic'), these products appear to be relatively safe. Although in excessively large dosages synthetic cannabinomimetics appear to cause

similar psychological effects as cannabis (paranoia, anxiety, emotional disturbance), studies have shown that it has no genotoxicity nor cytotoxicity (www.Mindfully.org, *JWH-018 Toxicity Report.* Sourced online, 20.05.2011). Even in extremely high doses in rats of 10mg/kg of body weight, no organ toxicity was detected (Psychonaut WebMapping Research Group (2009). *JWH-018 Report,* Institute of Psychiatry, King's College London: London, UK).

Although no conclusive data can be shown to show the safety of JWH-018, which is the most common of these synthetic cannabinomimetics, **there is no data of any kind, conclusive or otherwise, to show that these substances are toxic or harmful**. The only data that the Scheduling Advisory Committee based its claims of the dangers of these substances was **anecdotal**, which is clearly insufficient. Before these claims can be substantiated, much more research needs to be done. In my opinion, it is inappropriate to take a 'dangerous until proven otherwise' approach to the scheduling of new substances.

While JWH-018 appears to be safe, it is clear that, much like any other intoxicating OR therapeutic substance, in excessively large doses it can cause unpleasant and unhealthy effects. The potential for unpleasant side effects in excessive doses should not form the basis for banning a substance, as that would involve banning virtually every pharmaceutical on the market, even those freely available such as Panadol, and a number of food products, such as coffee, sugar, nutmeg, all of which have a much more clearly demonstrated organ toxicity that the substances in question.

Anecdotal evidence (in person and online) shows that while small doses are pleasant, relatively short-lived (compared to cannabis), and side-effect free (creating much less paranoia and anxiety than is common with hydroponic cannabis), excessive doses can cause paranoia, anxiety, heart palpitations and breathing difficulty. It is worth noting that despite the incredibly potent concentrations of these cannabinomimetics that are readily available online, no fatalities from these substances have been recorded. The recently much-publicised death in WA, where a man died shortly after consuming one of these products, was clearly media-hype, and in an article by the ABC, they mentioned that he died of unrelated causes.

On the other side of the fence, many people have found JWH-018 extremely helpful in overcoming cannabis addiction. One online user found JWH-018 the only successful tool in shaking off a cannabis addiction of 30 years. This is surely a valuable benefit of this product. Many other anecdotal accounts describe relief for extreme and chronic pain, and in fact it was while researching the pain-relieving properties of cannabis that these substances were discovered. Although at this stage the benefits of cannabinomimetics are unsubstantiated by scientific research, they appear to be significant, and merit further study.

Potential for Abuse

In respect to s52E(e) of the Therapeutic Goods Act, it appears that synthetic cannabinomimetics are non-addictive, which greatly increases their safety. Studies have shown that while repeated and consistent use of JWH-018 does lower sensitivity, no addiction has been reported (Psychonaut WebMapping Research Group (2009). *JWH-018 Report,*Institute of Psychiatry, King's College London: London, UK). No build-up of the substance has been shown to occur in the body (Psychonaut WebMapping Research Group (2009). *JWH-018 Report,*Institute of Psychiatry, King's College London: London, UK), and metabolism and excretion of the substance occurs normally (www.Mindfully.org, *JWH-018 Toxicity Report*. Sourced online, 20.05.2011).

Results of Banning

I assume that the intended outcome of scheduling these substances is reduced risk to the health and wellbeing of Australian citizens. If this assumption is correct, then the proposed scheduling will be counter-productive.

Outright banning of this substance will only encourage its misuse. If cannabinomimetics are forced into the black market, many producers will try to out-compete each other by creating the strongest versions possible, much as has happened with internet sales. This will surely increase the incidences of panic attacks and general negative effects. Furthermore, it will mean that the individual citizen may be denied the necessary information and help when dealing with this product. The criminal organisations will profit from a new area of trade opened up for them, the individual citizen will be disadvantaged and a revenue stream will be lost to the public purse, and to legitimate businesses.

Recommendations

My sincere recommendation is that JWH-018 and other similar cannabinomimetics are regulated under a new schedule altogether. This would be a holding category, where substances can be put before they are well understood. Sales are limited to adults, quality-control is imposed, and dosages / concentrations limited to safe levels. Advertising and availability could also be limited. The TGA could adopt New Zealand's Schedule D as a working model for a similar schedule in Australia, where inebriating, but low-risk substances could be regulated, and their access, advertising, sale

and use restricted appropriately. As the Schedules currently stand in Australia, I believe that JWH-018 could be scheduled under schedule 6, which is for *"Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label".*

My other key recommendation is that licensed vendors and their staff must undergo a training certificate such as 'Responsible Service of Intoxicating Substances', similar to the 'Responsible Service of Alcohol'. This would further increase the likelihood of positive experiences from this substance, and would place much greater responsibility with the stakeholders, who benefit from the sale of these substances.

Conclusion

The proposed schedule for JWH-018 and other similar cannabinomimetics is unreasonably harsh, and will be counter-productive. While most of the evidence that supports these substances is anecdotal and unscientific in nature, so too is the evidence that is being used by the TGA to decry them as harmful and dangerous. I propose that this is unacceptable, and that using a 'dangerous until proven otherwise' tactic is tantamount to treating humans as 'guilty until proven innocent' is not in line with the spirit of the Australian Constitution. More research is needed on both the dangers and benefits of these cannabinomimetics before a reasonable decision can be reached. The most logical way of dealing with them until such a time is to create a new Schedule as discussed above for unknown social inebriants.

[redacted]

PROPOSAL ON KAVA

BY

[redacted]

Overview

There is no clear-cut and serious attention to the religious, social, political, economic and medicinal behaviors of the ancient culture of kava ceremony in creating moral harmony and happiness with healthy environment among Moanana/Pacific Island migrants in Australia. This can give rise as well to the spirit of traditional altruism in sharing resources with those who are in need, and soothing the therapeutic concerns of the mind and body of kava drinkers. In addition, kava ceremony upholds almost all art forms in its unique mode of operation while drinking kava around the **kumete** (kava bowl), ranging from comedy, story-telling and oratory to music, poetry and myth-telling. In short, this social environment of kava is also traditionally considered by Moanan people as the fundamental essence of their overall cultures, surviving from ancient times, with its own rights should be preserved for future generations.

Why is this proposal?

This proposal aims to unfold certain views and information from two available and reliable primary sources regarding the ban of the culture of kava ceremony, and its increasing controversy and complication, in recent years throughout Australia and worldwide. The primary source is stemmed from papers and comments during the First Kava Conference [redacted] at the Australian National University in August 2011; and secondarily, from reviewing of available sources and findings on such a matter of great concern since the ACT National Multicultural Festival in Feburary 2011.

It is overall a result of studying and examining the Australian and world literatures, historical accounts and social realities on kava ceremony of the Moanan people and kava substance, and its relation to health, economic, political, religious and social issues on the local, national and international scenes. Consequently, [redacted] and its supporters have come up with the following issues of great concern for further consideration regarding the current ban of the culture of kava ceremony in the ACT, and its increasing controversy and complication in Australia:

- The culture of kava ceremony has been a victim of the increasing controversy and complication on kava tablets in medicinal and therapeutic terms throughout the recent health and pharmaceutical industries in Australia and Western societies;

- Western societies including their legal, health and pharmaceutical specialists have inclined to amalgamate such the issue of kavatablets and the culture of kava ceremony throughout in policy-making, laws and health guidelines, which should be treated differently in a fair manner;

- Kavalactones in kava mixing with other chemicals like acetone and ethanol can react and cause sudden health problems, even death, in human body, which is not the case in a situation of mixing kava and water in traditional Moanan way;

- Kavalactones in kava mixing with other chemicals like acetone and ethanol can react in bodies of non-Moanan people and cause sudden health problems, even death, because of no kava genetic elements in them;

- Kavatablets can help to relax and cure depression and anxiety if are used in wise and moderate manners and in accordance to correct health instruction and traditional Moanan knowledge and wisdom;

- Kavatablets in kava can cause sudden health problems, even death, if are not used in accordance to correct health instruction and traditional Moanan knowledge and wisdom;

- The current Australian Kava Laws are dealt largely with controlling the regulation of marketing of kavatablets and its protection, security and management but not with kava in traditional use;

- Kava substance in traditional Moanan method of mixing it with water can cause health and social problems if is abused and misused, as it can happen in other situations of abusing consumption substances like coffee and butter;

- Traditional kava consumption was never seen and considered as a process of abusing the mind and body until the allegation in the Northern Territory which claimed that kava was being abused and misused by the Aboriginal people;

- The traditional Moanan knowledge and wisdom on kava substance and its culture in terms of poetry, music, myth, oratory, comedy, dance, story-telling, story-myth and politics, have never been considered seriously by Western societies in the formulation of kava laws and medicinal and therapeutic laws in world market economy;

- The traditional Moanan knowledge and wisdom on kava ceremony in terms of poetry, music, myth, oratory, comedy, dance, story-telling, story-myth and politics are vital not only socially, politically and culturally but with the medicinal, therapeutic and psychological aspects of relaxing and soothing people as well;

- The traditional Moanan knowledge and wisdom show that kava substance can mix with water in different degrees of dilution in accordance to the nature of the ceremony, for example the degree of dilution for a funeral wake is different from a church's kava on Sunday before service, and so forth;

- The traditional Moanan knowledge and wisdom classify kava ceremony into about 40 different kinds of cultural, social, political, moral, religious, medicinal and therapeutic significance;

- The traditional Moanan knowledge and wisdom of kava myths spell out the place and specific obligations of children, youth, men and women in society;

- The traditional knowlwedge and wisdom of kava myths spell out some medicinal and therapeutic solutions for using kava and kavatablets in our modern era;

- There have not been any reliable and sufficient study in Australia and worldwide about the social, political, economic, moral, religious, medicinal, therapeutic and cultural significance of kava ceremony among Moanan migrants living in Western societies;

- The culture of kava in Australia and Western societies has created the new positive behaviour pattern of send remittances into the homelands, for example there are about 1000 Kava Tonga Clubs overseas who send about

150 million dollars a year to Tonga for socio-economic purposes to help relatives and friends who are in need;

- The culture of kava in Australia and Western sociaties has created the new positive behaviour pattern of donating to help those migrants living abroad who are in need;

- The culture of kava ceremony was banned in the ACT without consulting an dialoguing with its Moanan communities, but as a result of the claim that Aboriginal people of the Northern Territory misused and abused the substance;

- There was no study and survey of the culture of kava ceremony among Moanan people in Australia before formulating and legislating its ban, even though a number of studies were conducted only among Aboriginal people in the Northern Territory;

- There was no study and survey on how much kava are actually needed by Moanan people in Australia at large for their cultural and social consumptions, and how much kava to be imported per person, rather the 2 kg per person of 18 years old and above were decided by the authorities to use in the legislation since 2009;

- The culture of kava ceremony was banned in Australia due also to the increasing health problems, and even deaths, worldwide and with one death case in Australia as an aftermath of using kavatablets, but not a result of the traditional mixing of kava and water by Moanan people;

- There has been shortage of kava supply for Moanan people in Australia since the commercial ban of kava in quantities in 2009;

- The ban of kava ceremony is a violation of the human rights of Moanan people to exercise and practice their cultures in Australia;

- The ban of kava ceremony is a violation of the cultural rights of Moanan people in Australia which have been surving for more than thousand years;

- The ban of kava ceremony is a violation of the cultural rights of the Indigenous Moanan people of oceania;

- There was no democratic process prior to the formulation and legislation of Kava Laws in the ACT and Australia;

- The ban of kava ceremony is a violation of the UNCharters of Human Rights, Global Democracy and Indigenous Cultures of Moanan people of oceania;

- Some sections of the Medicines and Poisons Act (MPA) and Import Regulation Act 1956 (IRA) on kava at the Federal level are not in line with the 2008 Medicines, Poisons and Therapeutic Goods Act (MPTGA) of the ACT Government, in the sense that the formers still allow kava to be used for cultural purposes and 2 kg of kava to be imported by 18 years old and above into Australia, but not in the case of the latter;

- This has confused [redacted] and Moana people as a whole, which makes it difficult for them to find out which one to be followed between the Federal Kava Laws of the Commonwealth and the MPTGA of the ACT Government;

- Kava and alcohol cultures in the 2011 National Multicultural Festival were/are still a confusing issue for the AKMF and its supporters because the former was banned but not the latter with more social and health problems in Australia and worldwide;

- Alcohol kills about 3 000 Australians a year and only one died due to kavatablets and not kava with water extract, but the latter was banned at the Multicultural Festival rather than the former;

- Kava and alcohol are both used for medicinal and therapeutic purposes in a wise and moderated manner, and they can harm life if are abused and misused;

- The main problem among Moanan people in Australia and their youth is alcohol, and other illicit drug related matters, rather than the culture of kava ceremony;

- The culture of kava ceremony has been used by Moanan leaders and churches as a therapy and rehabilitation process for youth who escape from addicting to alcohol and other illicit drugs like heroine and ice;

- The issue of kava and alcohol has made [redacted] and its supppoters to feel that Kava Laws are discriminatory and suppressive of the culture of kava ceremony and not that of alcohol;

- This brings us to the issue of questioning the validity of the Australian Prohibition Laws in referring to kava as an illicit drug, or drug for that matter, which should not be the case;

- Is it valid to schedule kava as illicit drug while alcohol and cigarette are licit, but after all both of the latter are not natural but are mixed with other chemicals whereas the former is natural and is mixed with water per se in the situation of Moanan cultures;

- The issue of kava and alcohol has directed the attention of [redacted] and its supporters to feel being marginalized and isolated from any Multicultural and public function in the ACT since the National Multicultural Festival in February 2011.

Following the above issues of great concern, [redacted] and its supporters have felt that the ban of the culture of kava ceremony is unjust and undemocratic with scientific and academic inaccuracies. Generally, this has consequently caused the following side-effects within and among Moanan people, and between them and the Australian Governments in different ways.

Side-effects of the current Australian Kava Laws

The main side-effects of the current Kava Laws on Moanan/Pacific Island communities since 2004, particularly among kava drinkers in households, churches, traditional and modern functions are as follows:

- Increase in rate of kava beggars in Australian international airports and those in the homelands since 2009.

This kava ban has increased the rate of kava beggar in Australian international airports. It is a kind of social humiliation, degrading and marginalization of Moanan migrants. Moanans in Australian airports normally wait around there every day to ask and beg returning passengers from the Islands for 2 kg of kava, either as they arrive inland, or for passengers to leave the homeland airports to carry with them their 2 kg to relatives and friends in Australia.

- Increase in rate of illegal importation of kava into Australia at airports and wharfs.

This is also a well-known case among Moanan-Australians with a considerable number of court cases as well due to the increase rate of illegal importations and it is getting worst. Although the commercial importation of kava in quantities was banned in 2009, there are still huge amount of kava coming through the Australian airports and wharfs illegally without realizing them by customers.

- Increase in rate of black-market between the Eastern part and Northern Territory and Western Australia.

Since the emergence of kava controversy in the Northern Territory around the 1980's due to the allegation of increasing rate of substance abuse and health concerns among Aboriginal communities in the Arnhem Land, black-market has been radically flourishing and growing under-grounds between Eastern Australia and the Northern Territory and Western Australia. Some Moanan migrants and Aboriginal people have been arrested and appeared in courts, and some of them ended up in jails as a result.

- Possibility for kava boating to happen between the homelands and Australia.

We have collected reliable and sufficient information regarding the notion of kava boating, and it is already in daily conversation as a future option among some Moanan migrants. It is like a rumor in other parts of Australia that kava substance can be illegally brought into Australia by boating strategy. Historically speaking, Moanans will do whatever it takes to get some kava into Australia, and this fact will be witnessed soon if Australia continues in banning kava with more increasing restrictions on kava importation.

- Possibility of planting kava in Queensland, Northern Territory and Western Australia.

[redacted] has gathered reliable and sufficient information as well from the Moanan communities which show that there is a rumor and systematic plan to import live and raw

kava plants for the purpose of growing them in the Northern Territory, Western Australian and Queensland.

- Possibility of creating Moanan kava fanatics and extremists in Australia.

The current ban of the culture of kava ceremony in the ACT, and its increasing restrictions and controversy in Australia nationwide, can possibly create kava Moanan fanatics and extremists. [redacted] has received reliable and sufficient information from the Moanan communities on this matter, which will not be healthy and acceptable by the Federal and ACT Governments in the future.

Some suggestions for a solution

1. For the Federal and ACT Governments to allow the Moanan and Non-Moanans scientists and scholars from [redacted] and its wider research networks and communities to present their case studies on kava;

2. For the Federal and ACT Government to allow the Moanan and Non-Moanan anthropologists, sociologists, philosophers and pre-historians of [redacted] and its wider research networks and communities to present their studies of the ancient myths, oral traditions and cultures of kava in conjunction to scientific researches in our modern era;

3. For the Federal and ACT Governments to help [redacted] and its wider research networks and professionals to conduct independent studies in their Moanan languages of the risks and benefits of using kava in traditional ways throughout Australia;

4. For the Federal and ACT Governments to help [redacted] and its wider research networks and communities in conducting more public forums on kava with Moanan migrants throughout Australia;

5. For the Federal and ACT Governments to work with [redacted] and its wider research networks and professionals in drafting and producing a kava regulation in Australia for cultural Moanan purposes as such;

6. For the Federal and ACT Government to allow [redacted] and its research networks and professionals to run their new Educational-cultural Program on Kava throughout Australia particularly among the Aboriginal communities (please see the Attachment);

7. For the Federal and ACT Governments to include this Educational-cultural Program as part of the new regulation on kava, and treat the former as a continuing process, as it is seen in the situation of alcohol consumption, among other illicit and licit drugs;

8. The Educational-cultural Program is aimed too to combine and develop together the educational, cultural, health and legal significance of kava within and among Moanan, Aboriginal and Australian people as a whole into one full package of information.

[redacted]

[redacted]

GUIDELINES FOR EDUCATIONAL-CULTURAL PROGRAM ON KAVA

BY

[redacted]

[redacted] SETEMBER 2011

AIM:

The aim of this program is to help and educate any individual or organization in Australia about the traditional and modern Moana knowledge, and wisdom, on kava as a substance for physical consumption, medicinal-therapeutic uses and socialization, and kava as a culture for the preservation of moral unity and political harmony with aesthetic beauty.

METHOD:

This will be taught through ways of workshops, training, discussion, music, chants and story-telling during a given period for running the program, as well as, during the follow up to re-asses and direct the whole progress afterwards.

PROCEDURE:

This program is planned to run in different places throughout Australia by different trained and professional people from [redacted] and its research associates. It is seen as an on-going

process with its procedure that is based on the order of the 10 parts outlined below, and this can be used as part of a kava regulation in Australia to be enforced by Governments with the assistance and direction of [redacted].

The program is divided into 10 parts:

1. Preparation process & degree of dilution
2. Health and medicinal benefits
3 Social gathering or socialization
4. Arts of oratory, music, comedy, story-telling & therapy
5. Political and moral significance
6. Christian churches and spirituality
7. Cultural ceremonies
8. Myths and traditions with symbols
9. Genders in ancient and modern kava
10. Youth and children

The Program is planned to first run for six months in a form of workshop, training, practicing and dialogue; and then just observe, analyse and direct its progress for the next following 6 months. So it is one year altogether to run the whole training, but the overall Program if it is included as a regulation must be an on going process. It is largely based and built on traditional and modern Moanan wisdom and knowledge on kava as a substance and kava as a culture for survival.

However let us go through the detailed wisdom, knowledge and experiences in every individual Stage.

1. Preparation process & degree of dilution – a) Gear (Traditional & Modern - mortar and pestle and kava bowl, gloves & clean buckets and bowls including cups), b) Very concentrated & why, b) Concentrated, c) Less concentrated, d) Normal & e) Watery & why;

2. Health and medicinal benefits fall into the followings - a) Diet, b) Kava with water only, c) Body care, c) Sleep/Rest, d) Work/Exercise, e) Relaxing and Tightness, f) Stomach ache, g) Paralyse and prolong pain, h) Sore throat, i) Therapy;

3. Social informal gathering or socialization – Working kava (different kinds), after work kava, courting kava, dialogue/meeting kava, fundraising kava, and kava club or socialization;

4. Arts of oratory, music, comedy, story-telling & therapy – They are main arts that are practiced and repeated in most, if not all, kava social gathering;

5. Political and moral significance – Discipline & equal and reciprocal exchange of obligation under the customary principle of maintaining good relationship. This is where the essence and heart of obligation are kept alive in all kava levels of interaction;

6. Christian churches – Stories and traditions of the Catholic kava of priests and Methodist kava of ministers or preachers in the case of Tonga, and also the significance of kava in Moana old religion and modern religion of Christianity;

7. Cultural ceremony – Kava for coronation (Royal Kava Ceremony), instalment of a chiefly title, wedding, funeral, birthday, departure, arrival, war, competition, graduation, ordainment, etc;

8. Myths and traditions with symbols – Almost all types of kava are mythical oriented with their different but yet related traditions that symbolize very important Moanan beliefs and ways of life for over thousand years;

9. Genders in ancient and modern kava – This deals with clarifying issues on the social, political, economic, religious and moral significance of kava in ancient times between and within genders in comparison those of modern situation;

10. Youth and children – It is about the clarification of the place of youth and children in the whole process and situation of kava culture and its relation to their life in Australia especially between kava and alcohol, which the latter is the main problem among them but not the former.

CONCULSION:

This whole exercise is specifically to share with the public and Australians the full package in the development and preservation of the culture of kava in all levels, and because of the increasing controversy and complication of kava culture and kava substance in Australia, [redacted] and it supporters believe that this full package and guidelines of program, by unfolding the potentials and capabilities of kava culture for regulatory measures, may be considered and taken into account as an option on how to deal with such a matter of great significance in Australia and beyond.

[redacted]

2.2.7 Kava - submission 2 of 2.

Dear TGA, 21/8/11

Re submission on:

2.8 Piper methysticum (kava) - seeking advice on a proposal to allow access when used in accordance with the traditional use patterns of the Pacific Island region. Consideration may include exempting Piper methysticum from scheduling controls when in aqueous preparations for human non-therapeutic use (i.e. for recreational use).

[redacted] Thus, I hope my input into TGA submission 2.8 will be of benefit.

Firstly, kava use needs to be understood to be divided into a) medicinal use (i.e. tablets for anxiety) b) cultural use (i.e. traditional use by Pacific Island communities) c) recreational use (i.e. use by people for enjoyment- which is sometimes abused by some aboriginal communities).

The current law for medicinal kava use is adequate and well-balanced; The lack of a current law to protect cultural use of kava by Pacific Island communities is a significant issue that needs to be addressed; The current law for recreational use of kava is unbalanced- Western Australia and The Territories having kava banned is no solution, and this penalises some other members of the community who use kava occasionally as a relaxing substitute to alcohol. Furthermore, the current laws appear not to be entirely working some Aboriginal communities are still documented to abuse Kava with alcohol. This remains a public health issue as the high black market cost of kava reduces available money for food etc.

My proposed solution would be to overturn the 2kg limit of personal importation and replace with a 5Kg allowance, the ability for Pacific Island Kava clubs or licensees to be able to import dry raw kava into Australia, and for an opening up of kava sales to Western Australia (but maybe a state issue) and to Canberra. The Northern Territory is another issue and an alteration of the kava law should be met with greater vigilance in its prohibited use in “dry communities” and harsher penalties for black market sale. I would also advise for education and potentially a law to restrict kava drink driving. A certain amount is OK e.g. <5 bowls or 500mg of kavalactones (at an estimate) but when kava use is in excess it may inhibit motor skills.

I have no conflict of interest aside from voicing what I feel is a fair and just position. [redacted]

[redacted]

Clinical trials

1) Kava and St John’s wort in the Treatment of Major Depressive Disorder and Comorbid Anxiety: A Randomised Double-Blind Placebo Controlled Study.

2) Kava Anxiety Depression Spectrum Study (KADSS): A double-blind, placebo-controlled, cross-over clinical trial

3) The Kava Anxiety Lowering Medication (KALM Study): a) Acute anxiety RCT

4) The Kava Anxiety Lowering Medication (KALM Study): b) Chronic anxiety RCT

Kava Publications

Sarris et al. Acute Kava versus Oxazepam in Generalised Anxiety: Efficacy, Safety, and Genetic Correlates (in submission)

Teschke R, Sarris J, Schweitzer I (2011). Kava hepatotoxicity in traditional and modern use: The presumed Pacific kava paradox hypothesis revisited. *British Journal of Clinical Pharmacology* (accepted) ERA A

Sarris J, Teschke R, Stough C, Scholey A, Schweitzer (2010). Re-introduction of Kava (*Piper methysticum*) to the EU: Is there a Way Forward? *Planta Med* (in press) ERA B

Teschke R, Sarris J, Glass X, Schultes J (2010). Kava Hepatoxicity: Solution Back to Basics? *British Journal of Clinical Pharmacology* 71(3):445-8. ERA A

Sarris J, LaPorte E, Schweitzer I (2010). Kava (*Piper methysticum*): A Comprehensive Review of Efficacy, Safety, and Clinical Considerations. *Aust NZ Journal of Psychiatry* 45(1):27-35. ERA B

Teschke R, Sarris J, Lebot V (2010). Kava Hepatotoxicity Solution: A Six-point Plan for New Standardization. *Phytomedicine* 18(2-3):96-103. ERA B

Sarris J, Adams J, Kavanagh DJ (2010) An Explorative Qualitative Analysis of Participants' Experience of using Kava versus Placebo in an RCT. *Aust J Med Herbalism* 22 (1):12-16. ERA C

Sarris J, Kavanagh DJ, Bone KM, Adams J, Byrne G, Deed G (2009) The Kava Anxiety Depression Spectrum Study (KADSS): A Randomized, Placebo-Controlled, Cross-over Trial using an Aqueous Extract of *Piper methysticum*. *Psychopharmacology (Berlin)* 205(3):399-407. ERA A

Sarris J, Adams J, Wardle, J (2009) Time for a re-assessment of Kava in the treatment of anxiety? *Complementary Therapies in Medicine* 17(3):121-2 ERA A*

Sarris J, Kavanagh, DJ, Deed G, Bone KM (2009). St John's wort and Kava in the treatment of Major Depressive Disorder and comorbid anxiety: A randomised double-blind placebo controlled trial. *Human Psychopharmacology: Clinical and Experimental* 24, 41-48. ERA A

Sarris J, Kavanagh DJ (2009). Kava and St John's wort: Current Evidence for Use in Mood and Anxiety Disorders. *Journal of Alternative and Complementary Medicine* ERA A*

Sarris J, Kavanagh DJ, Adams J, Byrne G, Bone KM (2009) The Kava Anxiety Depression Spectrum Study (KADSS): A Mixed Methods Clinical Trial using an Aqueous Extract of *Piper methysticum*. *Complementary Therapies in Medicine* 17(3):176-8. ERA A

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Kava hepatotoxicity solution: A six-point plan for new kava standardization

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ABSTRACT

Kava-induced liver injury has been demonstrated in a few patients worldwide and appears to be caused by inappropriate quality of the kava raw material. When cases of liver disease in connection with the use of kava emerged, this was an unexpected and challenging event considering the long tradition of safe kava use. In order to prevent kava hepatotoxicity in future, a set of quality specifications as standard is essential for the preparation not only of kava drugs and kava dietary supplements in the Western world but also for traditional kava drinks in the South Pacific Islands.

For all these purposes a uniform approach is required, using water based extracts from the peeled rhizomes and roots of a noble cultivar such as Borogu with at least 5 years of age at the time of harvest. Cultivated in Vanuatu for centuries, noble varieties (as defined in the Vanuatu Kava Act of December 2002) are well tolerated traditional cultivars with a good safety record. At present, Vanuatu kava legislation is inadequately enforced to meet quality issues for kava, and further efforts are required in Vanuatu, in addition to similar legislation in other kava producing South Pacific Islands. Future regulatory and commercial strategies should focus not only on the standardization of kava drugs, kava dietary supplements, and traditional kava extracts, but also on thorough surveillance during the manufacturing process to improve kava quality for safe human use. The efficacy of kava extracts to treat patients with anxiety disorders is well supported, but further clinical trials with aqueous kava extracts are necessary.

We thereby propose a six-point kava solution plan: (1) use of a noble kava cultivar such as Borogu, at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) aqueous extraction, (4) dosage recommendation of ≤250 mg kavalactones per day (for medicinal use), (5) systematic rigorous future research, and (6) a Pan Pacific quality control system enforced by strict policing.

In conclusion, at different levels of responsibility, new mandatory approaches are now required to implement quality specification for international acceptance of kava as a safe and effective anxiolytic herb.

Introduction

The efficacy of kava (*Piper methysticum* G. Forster) as an anxiolytic herb has clearly been shown for ethanolic and acetonic kava extracts (Pittler and Ernst 2003; Sarris and Kavanagh 2009) as well as water based ones (Sarris et al. 2009b). In the past, however, concerns have been expressed that toxic liver disease may have been caused in association with the use of kava as herbal remedy and dietary supplement in Western countries (Denham et al. 2002; Teschke et al. 2003, 2008b; Lebot 2006; Teschke and Wolff 2009) or as a traditional recreational beverage in the South Pacific region (Russmann et al. 2003; Teschke et al. 2008a, 2009). Kava hepatotoxicity became part of the growing group of herbal hepatotoxicity with major clinical and regulatory challenges, observed in a few patients with causalities for kava ± comedication (Teschke 2010a,b; Teschke et al. 2010). Its worldwide appearance in patients originating from European countries, the United States, Australia, and New Caledonia was unexpected (Denham et al. 2002; Teschke et al. 2008a, 2009), since kava has been used for centuries without overt toxic liver effects in the South Pacific Islands (Lebot et al. 1997; Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Lasme et al. 2008). The international discussions centred on the question as to what extent kava may have been hepatotoxic due to poor kava quality (Schulze et al. 2003; Lebot 2006; Schmidt 2007; Teschke et al. 2008a; Sarris et al. 2009a; Teschke 2010b). Based on the worldwide interest and various uncertainties, inconsistencies and confounding variables associated with the reported cases of patients with kava hepatotoxicity, a thorough

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WHO report addressing these issues was mandatory (WHO 2007). Specific points of concern included the use of inappropriate kava plants and plant parts, solvents, solubilizers, adulterations, and impurities (WHO 2007; Teschke 2010b).

The aim of this report is to discuss future requirements at the legislation, regulatory and commercial level in connection with kava-induced liver injury and to propose a six-point plan for standardization of kava drugs, kava dietary supplements, and traditional kava beverages for safe human use.

Kava: traditional and modern use

The term kava refers to the plant native to the South Pacific Islands and its products derived from its rhizome and roots such as traditional kava beverages, kava drugs, and kava dietary supplements (Lebot et al. 1997; Denham et al. 2002; WHO 2007).

Plant

Vanuatu is considered as the origin of the kava plant which belongs to the family of Piperaceae (Lebot et al. 1997). The physiological properties of kava have been demonstrated to result from the kavalactone content and the chemotype commonly assessed in plants of the same species with genetically defined phytochemical characteristics (Lebot and Lévesque 1996; Lebot et al. 1997; Lebot 2006; Lasme et al. 2008). Six major kavalactones account for approximately 96% of the lipid extract and have been shown to be pharmacologically active (Lebot 2006).

Traditional drink

Kava as the traditional water based drink is an integral part of religious, social, economic and political life in the South Pacific region for centuries and usually well tolerated, unless overdosage with prolonged use prevails (Lebot et al. 1997; Denham et al. 2002; Schmidt et al. 2005; WHO 2007; Lasme et al. 2008). There have been some early restrictions for its use in Australia (WHO 2007) and recent legal definitions for planting, harvesting and marketing kava plants in Vanuatu to be used as traditional kava drinks (Vanuatu Legislation 2002).

Herbal drug

Until 2002 when the ban for kava-based products was issued, ethanolic and acetonic kava extracts had been sold as regulatory approved drugs in pharmacies without prescription in Germany and Switzerland; in the latter country they have also been available in drug stores since 1998 (Teschke et al. 2008a,b). Similarly, in other countries such as Austria, Belgium, Brazil, Canada, Ireland, Portugal, and the United Kingdom, kava-based products under regulatory control have previously been available either as drugs (Schmidt et al. 2005; WHO 2007), or as dietary supplements (WHO 2007). Regulatory approval for kava drugs was restricted to treatment for anxiety.

Dietary supplement

It is unclear to what extent kava was used as unregulated dietary supplement in Germany and Switzerland, since only one single report from Germany presented the case of a patient who treated herself with a powdered kava rhizome (Weise et al. 2002). In both and other countries, there was lack of regulatory approval for the use of kava dietary supplements (WHO 2007).

Classification of kava cultivars

In December 2002, the Vanuatu government passed the Kava Act No. 7 (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) which identifies and categorizes different cultivars into noble cultivars, medicinal cultivars, Two Days cultivars, and Wichmannii varieties.

Noble cultivars

A long history of commonly safe use as a traditional social beverage and lack of liver injury has been attributed to kava (Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Schmidt et al. 2005), especially to the noble varieties (Lebot et al. 1997).

Medicinal cultivars

Medicinal varieties are considered having a long and proven history of beneficial properties amongst traditional Pacific herbalists for a variety of specific therapeutic effects, although not primarily for recreational use (Food Standards Australia New Zealand, 2005). They have been used exclusively for medicinal products and dietary supplements, suggesting their causative role for liver toxicity observed in patients who used these extracts.

Two Days cultivars

Two Days kava cultivars ("Tu Dei" kavas, two days intoxication) have occasionally been used for kava drugs (Schmidt 2007) and are now banned as an export commodity (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005). Strong psychotropic effects occur with these cultivars, and they usually cause side effects such as nausea due to high amounts of the kavalactone dihydromethysticin (Lebot et al. 1997).

Wichmannii cultivars

"Wichmannii" varieties (*Piper wichmannii* is the wild species ancestor of the domesticated kava, *P. methysticum*) are now also banned for export (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005). These varieties usually elicit strong physiological effects and are not used in daily consumption in the Pacific Islands (Lebot et al. 1997).

Kava prior to the ban

Standardization

Prior to the regulatory ban of kava in 2002 for Western countries, there was lack of standardization of kava to be used as traditional beverage in South Pacific Islands (WHO 2007), although side effects due to prolonged kava use at high dosage were known in Pacific Islanders and Australian Aborigines for a long time (Mathews et al. 1988; Clough et al. 2003; Russmann et al. 2003; WHO 2007; Brown et al. 2007; Teschke 2010a). However, the risk of liver damage was directly related to the amount of kava consumed that was up to 700 mg a day in one study, and in another report 45% of the participants consumed alcohol (WHO 2007), considering alcohol as common risk factor (Li and Ramzan 2010). As observed in Western countries, toxic liver injury also after use of traditional water based kava drinks was rare (Teschke et al. 2008a). Inappropriate or lacking standardization prior to the kava ban in 2002 was evident for the use of traditional kava drinks at various levels. There was lack of regulatory standards in the South Pacific Islands, a concern expressed 2001 by the Secretariat of the Pacific Community

Table 1
Regulatory shortcomings regarding kava prior to the kava ban.

Items
1. Lack of standardization of the best kava cultivar(s) to be used for kava drugs
2. Absent standardization of minimum age of kava plant at the time of harvest
3. Absent declaration of the type of solvents and solubilizers to be used for kava drugs
4. Failure of standardization of the analytical method to quantify kavalactones in extracts
5. Undefined percentage content of individual kavalactones desired for kava extracts
6. Lack of prescription advice for kava drugs
7. Inappropriate surveillance at the level of farmers and manufacturers

For details see text and respective references.

in its report of Pacific kava, designed as a producer's guide (SPC 2001). As late as 2002, the Vanuatu government issued a Kava Act (Vanuatu Legislation 2002) which received approval by the Vanuatu Parliament only 6 years later following an amendment to this law. Finally, only in 2005 some food standards have been published (Food Standards Australia New Zealand 2005).

In Western countries such as Germany, a set of quality specifications for kava drugs has been developed as regulatory standards in the years before the ban was issued. The standards have been compiled by experts of the Germany regulatory agency in the German kava monograph (Commission E 1990) and were supplemented later on in the official German drug codex (DAC 1998). To summarize these previous standards, the ingredients of the kava extracts had to be derived from the peeled and dried rhizome (i.e. not exposed to light) of the kava plant, maximum daily use was 120 mg kavalactones for no longer than 3 months, and indications for kava extracts were anxiety, tension, and restlessness. Pregnancy, breastfeeding, and endogen depression were listed as contraindications.

Cultivar and chemotypes

Prior to the ban, efforts were not evident to clearly define the best kava cultivar(s) to be used. In Western countries and in the South Pacific Islands, neither regulators nor manufacturers or producers resolved this issue (Teschke et al. 2008a). As a result, they did not consider that the various cultivars may differ in their specific positive and negative effects, including those with possible hepatotoxic ones (Lebot 2006; Schmidt 2007; Lasme et al. 2008).

There have been various regulatory shortcomings regarding kava (Table 1). Kava is not a unique plant, and therefore represents a regulatory challenge. The regulatory kava monograph (Commission E 1990) and the official German Drug Codex (DAC 1998) did not allude to the existence of various kava cultivars and has never considered the abundance of kava strains as a regulatory safety issue before the kava ban. Uncertainties of the quality regarding the kava cultivars have been a matter of early and major concern (SPC 2001; Denham et al. 2002; Schmidt et al. 2005; Schmidt 2007; Lebot 2006; Teschke et al. 2008a,b). The possibility was not ruled out that the hepatotoxicity problems were, at least to some extent, a consequence of poor quality control caused by an extraordinary increase in the size of the kava market (WHO 2007). Concern has also been expressed that substandard kava cultivars such as Tu dei may have been exported (Lebot 2006; WHO 2007), and this was substantiated by analytical assessment for two retain samples from Germany (Schmidt 2007). The lack of product standardization and selection of kava cultivars of the best chemotype and kavalactone content has been recognized also by the Pacific Community (SPC 2001). In particular, there is no established physical or chemical quality specification for kava exported for pharmaceutical products.

Eighteen kavalactones have been isolated from kava extracts, but only the six major kavalactones are used to define a particular kava chemotype (Lebot et al. 1997; Lebot 2006; Schmidt 2007; WHO 2007): kavain (K), dihydrokavain (DHK), methysticin (M), dihydromethysticin (DHM), yangonin (Y), and desmethoxyyangonin (DMY). The individual kava chemotype may be established by a system of kavalactone signatures, attributing to each lactone a number in the sequence of its elution from the HPLC (high performance liquid chromatography) column (Fig. 1): DMY corresponds to 1; DHK to 2; Y to 3; K to 4, DHM to 5; and M to 6. When the figures are sorted in the sequence of decreasing quantities of individual lactones in the sample, a signature is formed by this method of chemotype coding. Based upon this assessment, it became evident that kava exists in form of more than 200 variant strains, commonly called cultivars. Moreover, the chemotype may vary between roots, rhizomes, and basal stems (Lebot 2006; Lasme et al. 2008). The multiplicity of kava cultivars used for medicinal purposes is the consequence of fragmentary standards of regulatory agencies and manufacturers (Commission E 1990; DAC 1998; SPC 2001; Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) and rarely allows causality attribution to a single kava cultivar (Schmidt 2007).

Plant part

According to the official producer's guide for Pacific kava, edited by the Secretariat of the Pacific Community in Suva, Fiji Islands, there are six products from the kava plant considered for planting, the local market, and exports: stems, basal stems, chips of the rhizome, peelings of the rhizome, roots, and residues (SPC 2001). Stems are defined as plant parts more than 20 cm above the rhizome, used only as planting material; basal stems represent the first 20 cm of the stem just above the rhizome; chips of the rhizome are made from the peeled rhizome or the lower stems to be used for drinking; peelings of the rhizomes include also the peelings of the basal stems, previously used for export to pharmaceutical manufacturers and for drinking; roots without specification of use; residues consisting of mixed small pieces of the other commercial parts, used for drinking. It is of note that products declared as rhizomes may also contain basal stems and thereby aerial plant parts. Therefore, inappropriate product declaration might have been a problem for European countries requesting rhizomes alone but not combined with basal stems.

The quality of the best parts of the kava plant to be chosen was a matter of another debate (SPC 2001; Schmidt et al. 2005; Lebot 2006; WHO 2007; Teschke et al. 2008a,b). For clinical trials, analytical studies, and experimental investigations a variety of kava plant parts have been used and evaluated in detail (Table 2). Kava extracts to be used in Germany as kava drugs should have been prepared from dried rhizome chips of the kava plant according to the German regulatory agency (Commission E 1990), and the rhizome should be peeled as communicated by the official German drug codex (DAC 1998). In some European countries, however, kava preparations have often been manufactured from the root peelings or kava stumps excluding the aerial peelings (Schmidt et al. 2005). In the South Pacific the kava roots are often peeled; the peelings potentially exported, and the peeled roots used to prepare the traditional aqueous extract for their own consumption. These observations led to the conclusion that kava preparations made from the whole peeled root, as used traditionally, could be less likely to cause hepatotoxicity (Schmidt et al. 2005); this favourable statement should also apply to the rhizome, the preferred regulatory plant part (Commission E 1990; DAC 1998).

Readily available information suggests the previous use of aerial parts (SPC 2001; Dragull et al. 2003; Lebot 2006; WHO 2007; Teschke et al. 2008a,b) such as stems (SPC 2001; Dragull et al. 2003;

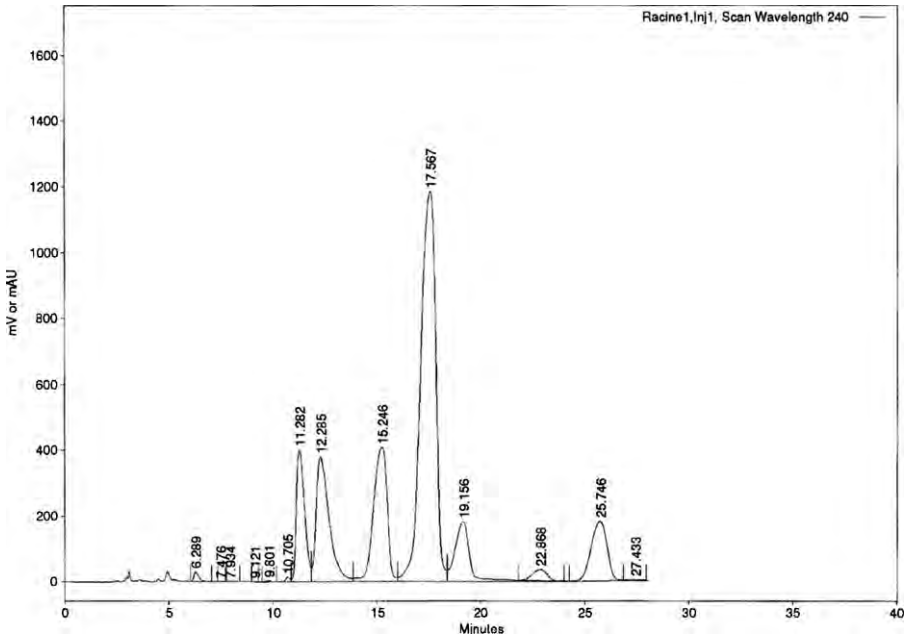

Fig. 1. HPLC chromatogram of the noble cultivar Borogu. There are six major peaks with retention times of 11.28, 12.28, 15.25, 17.57, 19.57, and 25.75 min, corresponding to desmethoxyyangonin, dihydrokavain, yangonin, kavain, dihydromethysticin, and methysticin, respectively.

Nerurkar et al. 2004; Lebot 2006) and leaves (Dragull et al. 2003) of the kava plant in the manufacturing process prior to the kava ban; these raw materials might have been taken instead of the usual rhizome. More specifically, according to the WHO report German pharmaceutical industries preferred to buy kava stem peelings to extract kavalactones to make kava drugs; kava stem peelings were sold at almost one-tenth of the price of kava roots (WHO 2007). It was also argued that commercial crude drug material that may have been adulterated by stem peelings and leaves, could possibly introduce the alkaloid pipermethystine into the commercial drugs (Dragull et al. 2003; Lebot 2006; WHO 2007), but recent analytical studies showed the absence of pipermethystine, at least in a series of retained samples of finished kava products from the German market (Lechtenberg et al. 2008). Nevertheless, uncertainty remains that the quality of commercial kava extracts may have varied from one batch to the other, and quality control of kava raw products was possibly not stringent enough. Uncertainty also exists regarding use of adventitious roots, originating from the stems and extending directly into the soil; they develop quite easily and are considered as valuable due to their high kavalactone content (SPC 2001). Undoubtedly, adventitious roots are aerial plant parts, not recommended for human use.

Extraction media and solubilizers

Prior to the kava ban, ethanol, acetone, and water have preferentially been used as media for kava extracts, but there was no regulatory statement which medium may be superior (Commission E 1990; DAC 1998). There was also no regulatory definition of the desired percentage of the kavalactones in the extracts. Various solubilizers such as macrogol, craspovidon, mentha oil, methyl acryl acid polymer and polysorbate polyols have been included in the extracts; all of them lack a regulatory recommendation of the best one to be used (Teschke et al. 2008a).

Daily dosage and duration of use

Prior to the ban, the daily dose was limited to 60–120 mg kavalactones according to the German kava monograph (Commission E 1990), but this statement has been subject of some specific considerations (Schmidt 2007; Teschke et al. 2008a). The previous regulatory recommendation for the maximum dose of 120 mg kavalactones is not sufficiently qualified since the analytical method for quantification has not been described (Commission E 1990); but it appears that TLC (thin layer chro-

Table 2
Compilation of kava plant parts used as raw material for various purposes.

Kava plant part
1. Rhizomes/syn. rootstocks (SPC 2001; Loew and Franz 2003; Dragull et al. 2003; Ernst 2004; Food Standards Australia New Zealand 2005; Weiss et al. 2006; Teschke et al. 2008b)
2. Rhizomes, fresh (WHO 2007)
3. Rhizomes, dried (Weise et al. 2002; Dragull et al. 2003; WHO 2007)
4. Rhizome roots (Brown et al. 2007)
5. Roots (SPC 2001; Dragull et al. 2003; Moulds and Malani 2003; Nerurkar et al. 2004; Lebot 2006; Brown et al. 2007)
6. Roots, fresh (Denham et al. 2002; Loew and Franz 2003; Currie and Clough 2003; WHO 2007)
7. Roots, dried (Denham et al. 2002; Currie and Clough 2003; Moulds and Malani 2003; Schmidt et al. 2005; Weiss et al. 2006; WHO 2007; Brown et al. 2007)
8. Roots, decorticated (Loew and Franz 2003)
9. Root barks, fresh and dried (Denham et al. 2002)
10. Roots, adventitious (SPC 2001)
11. Stems, including lower ones (SPC 2001; Currie and Clough 2003; Lebot 2006)
12. Stem peelings (SPC 2001; Dragull et al. 2003; Lebot 2006)
13. Stumps, including peelings (Ernst 2004, 2007; Lebot 2006)
14. Leaves (Dragull et al. 2003; Ernst 2004)

A variety of kava plant parts have been used and evaluated for clinical trials, analytical studies, and experimental investigations.

Table 3
Proposals for future strategies.

Recommendations
1. Vanuatu legislation regarding the preferred noble cultivar(s) such as Borogu
2. Additional legislation of peeled rhizome and roots to be used for water based kava extracts
3. Corresponding legislation also in other countries of the South Pacific Islands
4. Regulatory definition of noble cultivar such as Borogu and use of its peeled rhizomes and roots
5. Regulatory standardization of quantitative method for kavalactones in the extract
6. Limitation of kava use to water based extracts
7. Regulatory definition of daily dose and duration of use
8. Mandatory prescription guidance for kava drugs to minimize risks
9. Regulatory surveillance of cultivators, harvesters, farmers, and manufacturers

For details see text and respective references.

matography) was used (Loew and Franz 2003). As there are major quantitative differences, for instance, between TLC and HPLC (high performance liquid chromatography), accuracy is lacking (Schmidt 2007). Therefore, a dose of 120 mg kavalactones assayed by TLC corresponds to 170 mg quantified by HPLC. German drug companies were not obliged to note the used method to quantify kavalactones in their drugs, and it remained unclear whether 120 mg kavalactones in their products reflect assessment by TLC or HPLC. On a clinical basis, most patients with verified kava hepatotoxicity used a daily overdose of kavalactones (Teschke et al. 2008a,b, 2009).

For the use of traditional kava beverages, there was no regulation regarding maximum length of usage (Food Standards Australia New Zealand 2005). Treatment duration no longer than 3 months was advised for kava drugs by the German regulatory agency (Commission E 1990), but prolonged treatment was usual (Teschke et al. 2003, 2008a,b; Schmidt et al. 2005; WHO 2007).

Future strategies for standardization

It was in the overall interest to further investigate any legitimate hypothesis concerning kava' toxicity in order to attempt either to exonerate some forms of kava, or to provide recommendations that will assure their safe use (Richardson and Henderson 2007). Recently, pathogenetic aspects of kava hepatotoxicity have been reviewed in detail (Teschke 2010b); strategies have now to be developed to minimize hepatotoxic risks of kava products (Table 3), with some proposals made in the past (Schmidt et al. 2005; Lebot 2006; Schmidt 2007; WHO 2007; Richardson and Henderson 2007; Teschke et al. 2008a). The kava problem was not limited to the kava pharmaceutical markets such as Germany and Switzerland (Schmidt et al. 2005; Teschke et al. 2008a,b), but is extended to the kava dietary supplement markets with polyherbal kava mixtures such as the Unites States and Australia, and also to the traditional kava markets like New Caledonia in the South Pacific Islands (Russmann et al. 2003; Teschke et al. 2008a, 2009; Schmidt 2007; WHO 2007). Therefore, an overall approach to standardization of kava extracts to be used as drugs, dietary supplements, and traditional drinks needs to now be mandatory.

There is an urgent need of standardization, primarily at both the legislation and regulatory level, followed at the commercial level. The WHO report criticized the lack of accepted standards for the growth of kava, collection practices, and supply of raw material for medicinal purposes (WHO 2007). There is also inadequate quality control in the selection of the appropriate plant parts of kava, in the collection of the appropriate plant parts and in the preparation and testing of the raw materials. Quality control should include analytical verification of the chemotype using HPLC (Lebot and Lévesque 1996; Lebot et al. 1997; Siméoni and Lebot 2002; Lasme et al. 2008) or the recently described method of near-infrared reflectance spectroscopy (NSIR) (Lasme et al. 2008); the NSIR system has been calibrated for the six major kavalactone content measurements. To meet safety concerns, all involved parties starting from the patient and general consumer down to the cultivator and farmer are well advised to contribute to the overall goal of improving the safety of kava use. We thereby propose a kava solution plan as outlined subsequently.

Six-point kava solution plan

There are several key elements of the proposed six-point kava solution plan: (1) use of a noble kava cultivar such as Borogu that is at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) aqueous extraction, (4) dosage recommendation of $\leq$250 mg kavalactones per day (for medicinal use), (5) systematic rigorous future research, and (6) a Pan Pacific quality control system enforced by strict policing.

(1) Noble cultivar

There is little clinical and experimental support to suggest medicinal kava cultivars as the variety of choice for kava drugs, kava dietary supplements, and traditional kava drinks since these varieties have previously been associated with toxic liver injury. But how is the ideal kava extract to be defined? Kava cultivars with a long history of safe use as a traditional social kava beverage in the South Pacific Islands should ideally be chosen. These criteria are basically met by a few noble cultivars (Lebot 2006; Schmidt 2007; Lasme et al. 2008), as classified by the Vanuatu Kava Act (Vanuatu Legislation 2002) and listed with all details subsequently (Food Standards Australia New Zealand 2005). Accordingly, good candidates in alphabetical order are primarily the listed noble kava cultivars (Table 4).

In the past, the chemotype of the preferred cultivar has not yet definitively been determined, but suggestions have been made (Schmidt 2007; WHO 2007; Food Standards Australia New Zealand 2005; Sarris et al. 2009b). It should be one with a high relative content of kavain (Lebot 2006; Schmidt 2007; Sarris et al. 2009b), considering also its advantageous lack of P450 inhibitory properties and preventing thereby possible interactions with drugs (Mathews et al. 2002); dihydrokavain may be necessary in amounts sufficient to mediate the anxiolytic properties of kava (Amorim et al. 2007); recommendations include also low amounts of methysticin (Mathews et al. 2002; Schmidt 2007), desmethoxyyangonin (Schmidt 2007), and eventually dihydromethysticin (Mathews et al. 2002). These criteria are not generally met by all previous medicinal cultivars used for German and Swiss kava drugs alleged to cause toxic liver disease; such as chemotypes 526431, 462531, 254631, and 246531 (Schmidt 2007). Possible candidates are cultivars with a chemotype signature of 423561 or 425361, with high amounts of kavain and dihydrokavain and low amounts of methysticin and desmethoxyyangonin.

Based on the opinion of local experts, the noble kava cultivar Borogu with the chemotype signature 423561 is now one of the preferred kava varieties (Lasme et al. 2008) and may easily be identified by a typical HPLC chromatogram (Fig. 1). According to the chemotype, Borogu has a high content of kavain and in order of decreasing amounts dihydrokavain, yangonin, dihydromethysticin, methysticin, and desmethoxyyangonin (Siméoni and Lebot 2002; Lasme et al. 2008); its chemotype is identical for both roots and rhizomes (Lasme et al. 2008), allowing the use of the two plant parts. Cultivated with a long tradition in Vanuatu (the area of origin of *Piper methysticum*), Borogu is well established for daily drinking

Table 4
Noble kava cultivars of Vanuatu.

Noble cultivar	Origin	Chemotype
Ahouia	Tanna	426531
Amon	Tanna	246513
Asiyai	Aneityum	246531
Bir Kar	Santo	246513
Bir Sul	Santo	246531
Biyai	Aneityum	426531
Borogoru	Maewo	425361
Borogu	Pentecost	423561
Gegusug	Gaua	246531
Ge vemea	Vanua Lava	245631
Ge wiswisket	Gaua	246513
Kelai	Epi	423516
Leay	Tanna	246351
Melomelo	Ambae	245361
Melmel	Pentecost	246531
Miela	Emae	426351
Naga miwok	Vanua Lava	246351
Olitao	Emae	245631
Palarasul	Santo	246531
Palasa	Santo	246531
Paliment	Emae	426351
Pia	Tanna	423516
Poivota	Santo	243561
Pualiu	Tongoa	246531
Puariki	Tongoa	423156
Sese	Pentecost	245631
Silese	Malekula	423651
Urukara	Santo	426531

Alphabetical order of noble kava cultivars in Vanuatu with their place of origin (Vanuatu Legislation 2002; Food Standards Australia New Zealand 2005) and their chemotype assessed in their roots. The numbers of the chemotypes correspond to the following kavalactones: 1, desmethoxyyangonin; 2, dihydrokavain; 3, yangonin; 4, kavain; 5, dihydromethysticin; and 6, methysticin. The data are based on original studies (Lebot and Lévesque 1996; Lebot et al. 1997; Siméoni and Lebot 2002) and substantiated by recent reports (Lebot 2006; Lasme et al. 2008). As far as a cultivar keeps its chemotype fingerprint 42. . . or 24. . ., then it is a "noble" cultivar. Other requirements are that (1) there are no parts exposed to light in the raw material, (2) it is organically grown, (3) all the parts are well identified and separated, (4) it is sufficiently old (5 years for export), (5) and the village or origin is known (traceability) (Vanuatu Legislation 2002).

without apparent side effects and is known for its rapid effect, thus a potential ideal candidate for future clinical studies. Regulatory kava standardization regarding the best noble kava cultivar(s) such as Borogu to be used for both traditional and medicinal purposes is mandatory, should kava enter the pharmaceutical market again.

(2) Peeled rhizomes and roots

The kava WHO Report differentiates the rhizome from the roots and clearly defines the rhizome as the kava part below the stem and above the roots (WHO 2007). At least for future kava drug manufacturing in Western countries, the rhizomes and underground roots (excluding the adventitious ones) may be used; they should be peeled and their chips be dried. At the local manufacturing level, however, uncertainties remain due to vague legislation.

The Vanuatu Kava Act No. 7 of 2002 describes some protection rules of kava for export which include kava drugs and kava dietary supplements (Vanuatu Legislation 2002). Excluded from export are stumps, shoots, growing buds, lateral branches, and other planting materials of kava, as well as fresh plant parts such as roots or stumps that could be used for propagation. Kava or kava products may only be exported when each of the following is clearly marked on it: name of the variety, island of origin, distinct organs of the kava, and the words "Original Vanuatu Kava". In essence, any part of the kava plant may be exported, as long as labeling conforms to the legislation. The labeling does not require the information whether the plant part is peeled or not; nor whether peelings are to be exported. This leads to the conclusion that neither the peeled rhizome nor the rhizome itself is a legislative issue in Vanuatu. Additional legislative efforts are therefore necessary to ensure that only peeled and dried rhizomes and roots are exported to be used for kava drugs and dietary supplements. Surprisingly, Vanuatu Kava legislation differentiates between kava quality requirements for local use and those for export. For example, minimum maturation time for the kava plant at harvest is 5 and 3 years for export purposes and for local markets, respectively. To circumvent possible mix-ups and associated quality problems of kava products considered for export, legislation for quality specifications should be identical for both the local and the international markets.

(3) Aqueous extraction

Since hepatotoxic reactions were observed with traditional aqueous kava extracts as well as ethanolic and acetonic extracts, the used solvents appear to play no major role for the observed hepatotoxicity (Teschke et al. 2008a; Teschke 2010b). However, to be on the safe side, aqueous kava extracts should be given preference rather than extracts prepared with chemical solvents. The Kava WHO Report has recommended the use of water based kava extracts for medicinal and recreational purposes in analogy to traditional aqueous kava beverages (WHO 2007). This proposal should commonly be followed, an initial study with aqueous kava extracts already showed preliminary results of safety and efficacy in treating patients with anxiety symptoms (Sarris et al. 2009b, 2010a).

(4) Daily dose and duration of treatment

With the introduction of water based kava extracts for kava drugs and dietary supplements, new regulatory challenges emerge regarding the daily dose of kavalactones to be recommended. Regarding ethanolic and acetonic kava extracts, the upper limit in Germany was 120 mg kavalactones per day before the kava ban (Commission E 1990), determined by TLC and not by HPLC (Loew and Franz 2003). In Australia the maximum daily dose of kavalactones allowed for registered aqueous kava extracts to treat anxiety disorders is limited to 250 mg, quantified by HPLC (Sarris et al. 2009b). This value is considerably lower than the use of 2500 mg kavalactones ingested with traditional water based kava beverages per day in the South Pacific Islands; under these conditions hepatotoxic side effects occurred (Russmann et al. 2003; Teschke et al. 2009). Thus, an appropriate safety range is necessary to be on the side of caution. Some uncertainties pertain to the duration of treatment with aqueous kava extracts which was 4 weeks and thus only short term (Sarris et al. 2009b). At present, therefore, defined standards for daily dose of kavalactones and duration of therapy are lacking and have to be established.

(5) Future research

It is well recognized that further clinical trials with aqueous kava extracts are necessary to firmly establish water based kava extracts as effective and safe therapy options for anxiety disorders (Sarris et al. 2010b). The raw material for the aqueous extracts should be derived from peeled and dried rhizomes and underground roots (i.e. non adventitious) of a noble kava cultivar such as Borogu (Lasme et al. 2008), matured for at least 5 years (Vanuatu Legislation 2002). These clinical studies should determine efficacy, possible side effects including hepatotoxic ones, and the maximum of both daily dose of kavalactones and duration of therapy (Sarris et al. 2010b). Safety data derived from clinical studies with water based kava extracts may easily be transferred to traditional used aqueous kava extracts, provided the set of quality specifications such as the noble kava cultivar and the use of peeled rhizomes and roots are identical for both conditions. For clarification of the

discrepancies aroused by allegedly hepatotoxic reactions of some kava preparations, additional studies have to be performed with the new cultivar preparations in comparison with the former kava extracts. These studies should comprise chemical standardization and molecular biological investigations inclusive genomic studies. Attention should be paid to pipermethystine (WHO 2007) and flavokavain B (Zhou et al. 2010) as possible culprits for kava hepatotoxicity (Teschke 2010b). There is also the urgent need to prove or disprove aflatoxin contamination of the kava raw material as a possible mechanism for the observed liver toxicity in a few patients.

(6) Legislation, regulatory standards, and commercial surveillance

Strict standards for safe use of aqueous kava extracts as herbal drugs, dietary supplements and traditional drinks have to be established by legislation in the South Pacific Islands and by regulatory agencies of countries involved in the cultivation and farming of kava plants as well in the production and distribution of kava extracts. New legal and regulatory approaches including strict commercial surveillance are mandatory since traditional aqueous kava extracts may not necessarily be devoid of side effects. Kava has the potential of reconsideration as an approved herbal drug for effective and safe treatment of anxiety, but further steps are now required.

Conclusions

Based on the experience with hepatotoxic side effects due to the use of aqueous, ethanolic, and acetonic kava extracts, as well as herbs–kava mixtures in a few patients, efforts have to be undertaken to improve kava quality. Suggestions have been made to use water based extracts of peeled rhizomes and roots derived from a noble kava cultivar such as Borogu planted at least 5 years before harvest. This set of quality specifications should be used as standard not only for kava drugs and kava dietary supplements in Western countries but also for the traditional kava drinks in the South Pacific Islands. In addition, there is an urgent need to establish strict legal and regulatory surveillance of kava cultivators, farmers, harvesters, and manufacturers. Further clinical trials with aqueous kava extracts are necessary to confirm efficacy and lack of side effects in patients with anxiety disorders. Provided these studies are promising, a return of kava to Western countries is feasible. It is intended that the six-point kava solution plan we propose will advance the research, development and supply of kava globally and eventually lead to the return of kava to restricted markets.

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Re-introduction of Kava *(Piper methysticum)* to the EU: Is There a Way Forward?

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- kava
- *Piper methysticum*
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- kava hepatotoxicity
- anxiety
- generalised anxiety disorder
- pharmacogenomics

Abstract

Kava (*Piper methysticum*) is an effective anxiolytic that has been withdrawn from various consumer markets in European countries due to concerns over its hepatotoxicity. It is plausible that the reported hepatotoxicity may be due in part to plant substitution, or an incorrect cultivar, or plant parts being used (such as leaves or bark); thus both the plant chemotype and the plant part used may be critical factors. If re-institution of kava in the EU is to occur, more evidence is required to determine its safety and efficacy. Furthermore, according to current evidence, the study of traditional water soluble rhizome extracts using a noble cultivar of kava may be advised. The Kava Anxiety-Lowering Medication (KALM) project is due to start in late 2010 to address these considerations. The KALM project uses an aqueous rhizome extract of a noble cultivar of kava in participants with generalised anxiety and Generalised Anxiety Disorder (GAD). The project comprises of 1) an acute RCT, kava (180 mg of kavalactones) versus oxazepam and placebo in 20 anxious people, testing effects on cognition, mood, anxiety, and driving; 2) an 8-week RCT comparing kava (120 mg kavalactones) versus placebo in 100 patients with GAD. To assess differences between dosages, non-responders at 3 weeks will be titrated to 240 mg of kavalactones. The project will also assess the effects of kava on liver function tests and its side effects profile. A novel component of the project is the pharmacogenomic exploration of phenotypical responses (GABA system and cytochrome P450 markers). The results of the study may be of benefit to sufferers of anxiety and the future economy of the Pacific islands, potentially providing an important step in the way forward with kava.

Abbreviations

HAMA:	Hamilton Anxiety Rating Scale
KADSS:	Kava Anxiety Depression Spectrum Study
KALM:	Kava Anxiety-Lowering Medication Project
MADRS:	Montgomery-Asberg Depression Rating Scale

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Overview

There is compelling supportive evidence for the use of kava (*Piper methysticum*, Forst. f., Piperaceae) as a monotherapy treatment for anxiety, with several reviews and meta-analyses revealing statistically significant anxiolysis compared with placebo [1,2]. However, concerns over hepatotoxicity have led to its withdrawal or restriction in many countries including European ones [3,4], whereas kava extracts are currently available in the United States, Australia, and the South Pacific Islands [5]. It appears therefore that the hepatotoxic risks of kava extracts are being evaluated differently by the individual countries.

At the clinical level, a variety of data on cases of patients with kava hepatotoxicity has been gathered [5]. It is a rare disease and occurs not only with ethanolic and acetonic kava extracts, but also with aqueous ones [6]. Confounding variables and risk factors included concomitant use of other herbal drugs and dietary supplements, as well as synthetic drugs, daily overdose, and prolonged treatment [7]. Kava-induced liver injury was mostly of the hepatocellular type rather than cholestatic or mixed. Causality assessment for kava was complicated in various cases not only due to confounding variables, but also from alternative diagnoses that were overlooked in the course of regulatory evaluation. As a consequence, in only

a few patients causality for kava could be established, mostly in combination with co-medication [7].

Regarding the mechanistic aspects of kava hepatotoxicity, several theories have been advanced and evaluated. They comprise metabolic interactions with exogenous compounds at the hepatic microsomal cytochrome P450 level, alcohol abuse, genetic enzyme deficiencies, toxic constituents and metabolites derived from the kava extract including impurities and adulterations, cyclooxygenase inhibition, P-glycoprotein alterations, hepatic glutathione depletion, solvents and solubilisers of the extracts, and kava raw material of poor quality [8–15]. In respect to metabolic interactions between kavalactones and the other exogenous substrates at the level of the hepatic microsomal cytochrome P-450 [6], its isoenzymes are not inhibited *in vitro* by kavain, however other kavalactones have been found to reduce the microsomal metabolism of exogenous compounds, which are not only substrates, but also inhibitors or inducers of P450 [3, 10]. The majority of patients with suspected kava hepatotoxicity co-medicated (commonly with up to five different pharmacotherapies) [6]. Theoretically, the metabolism of co-medicated drugs could be altered in such a way that even relatively benign compounds may exert hepatotoxic effects. Although it is conceivable that in some patients kavalactone-drug interactions may be a contributory factor, there is currently little clinical evidence of it. Other kava constituents including pipermethysticine and flavokavins A, B, and C may also be implicated in hepatotoxicity; however, these are not found in the extracts used in previous kava product analyses, and the data backing this theory are not definitively supported [16].

After kava ingestion, some kavalactones are excreted from the body unchanged via urine and bile [17]. However, before elimination, toxic alterations of the liver cells may potentially occur. It should be noted that there is little experimental evidence that kavalactones (in clinically relevant or even higher doses) may be hepatotoxic themselves. The next aspect pertains to whether enzymatic degradation of kavalactones to their metabolites may exert hepatotoxic properties. Urinary samples in humans after ingestion of aqueous kava extracts showed the appearance of kavalactone metabolites, and further analysis of these products revealed various enzymatic transformations, which include: reduction, demethylation, and hydroxylation [17]; this is in line with the proposed enzymatic breakdown of kavalactones via reduction and hydroxylation [18]. Views have been expressed by others that kavalactones may indeed be substrates of P450 (or more specifically of its isoenzyme P450 2D6), but firm evidence is still lacking [17, 19]. In conclusion, the possible involvement of hepatic microsomal cytochrome P450 for the enzymatic breakdown of kavalactones into toxic metabolites requires further experimental assessment.

Regardless of the toxicological mechanism(s) to be established in experimental studies, the primary issue now concentrates on solvents and kava quality. Certainly, extraction media may change the pattern of kavalactones and other constituents in the resulting kava extracts [20]; but hepatotoxic reactions have been observed with all extraction media used (though possibly with higher rates when organic solvents have been used compared to aqueous extracts) [5]. These findings suggest that major concerns relate to the plant quality rather than to solvents. Six major kavalactones comprise of 96% of the lipophilic resin compounds of the plant, and are used to define kava chemotypes, serving as a marker for quality [21]: kavain (K), dihydrokavain (DHK), methysticin (M), dihydromethysticin (DHM), yangonin (Y), and desmethoxyyangonin (DMY) [22]. Individual kava chemotypes may be elucidated by a system of kavalactone signatures via high pressure liquid chromatography, or near-infrared reflectance spectroscopy analysis [23]. In the Lebot and Lévèsque (1996) system the six major kavalactones correspond to DMY (**1**); DHK (**2**); Y (**3**); K (**4**); DHM (**5**); M (**6**), yielding a six figure chemotype e.g. 423 651 [22]. A good kava quality can be expected for kava cultivated varieties (cultivars) consumed traditionally for centuries by the people of the South Pacific Islands [24]. These cultivars are named "noble", have a sound safety record, and may be consumed on a long term on a day-by-day basis. According to Lasme and colleagues [23], good candidates (in alphabetical order) are the ones from the noble kava cultivars in Vanuatu such as: Ahouia, Amon, Asiyai, Bir Kar, Bir Sul, Borogoru, Borogu, Biyai, Gegusug, Ge vemea, Ge wiswisket, Kelai, Leay, Melomelo, Miela, Melmel, Naga miwok, Olitao, Palarasul, Palasa, Paliment, Pia, Poivota, Pualiu, Puariki, Sese, Silese, and Urukara.

A daily consumption of 2500 mg kavalactones is common for these noble kava cultivars in traditional recreational use [6], which is much higher than the value of up to 120 mg recommended previously for European countries. Other cultivars such as "medicinal", "tudei", or "wichmanni" varieties are used; however, these varieties are not commonly consumed by the people in the South Pacific Islands for recreational use as they have less pleasant effects than noble cultivars [24]. Chemotypes starting with "423" such as the Borogu, Malog velablalas, or Nikawa Pia, with high kavain and relatively lower dihydromethysticin, may be recommended. These cultivars also yield a reasonable amount of total kavalactones of between 10–15% [23]. Other quality issues involve the use of various plant parts such as aerial, stump, stem, adventitious roots, bark, and rhizome, all of which have different levels of kavalactones [21]. The peeled rhizome traditionally used is higher in kavalactones than other parts and absent of pipermethysticine [8, 23].

In response to safety concerns, the World Health Organisation commissioned a report assessing the risk of kava products [5]. Recommendations from this report suggest that products from water-based suspensions should be developed and tested in clinical studies, and that these formulations should preferentially be used over acetonic and ethanolic extracts. This approach is supported theoretically by evidence of safety from traditional use, and because aqueous extracts are rich in hepatoprotective glutathione [19]. While it seems a commonsense approach to adhere to the traditional usage of the plant, it should, however, be noted that five cases of hepatotoxicity have been documented involving traditional water soluble extracts [6]. Unfortunately, in none of these cases a batch analysis of the incriminated kava extracts has been made. Despite this uncertainty, it is plausible that the observed hepatotoxicity may be due to plant substitution or an incorrect cultivar, or plant parts being used (such as leaves or bark); thus both the plant chemotype and the plant part used may have been critical factors in hepatotoxicity.

The KALM Project

For the safety and efficacy of kava as an anxiolytic to be re-established for potential re-institution of kava in the EU, more studies are required to determine the effects of doses between 120 mg and 240 mg. As detailed above, the current evidence supports the study of a traditional water soluble peeled rhizome extract of a noble cultivar of kava, however, further evidence of safety and efficacy of this preparation is required. A study on kava and

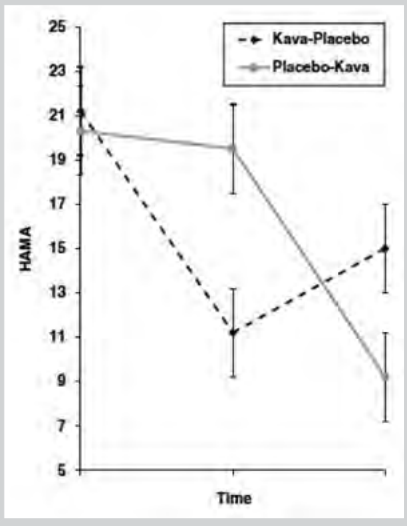

Fig. 1 Reduction of anxiety on Hamilton Anxiety Scale (HAMA) over two 1-week periods using 250 mg of kavalactones per day versus placebo (cf. ref. [26]). Patients in group 1 were prescribed kava for one week then placebo; patients in group 2 were prescribed placebo then kava.

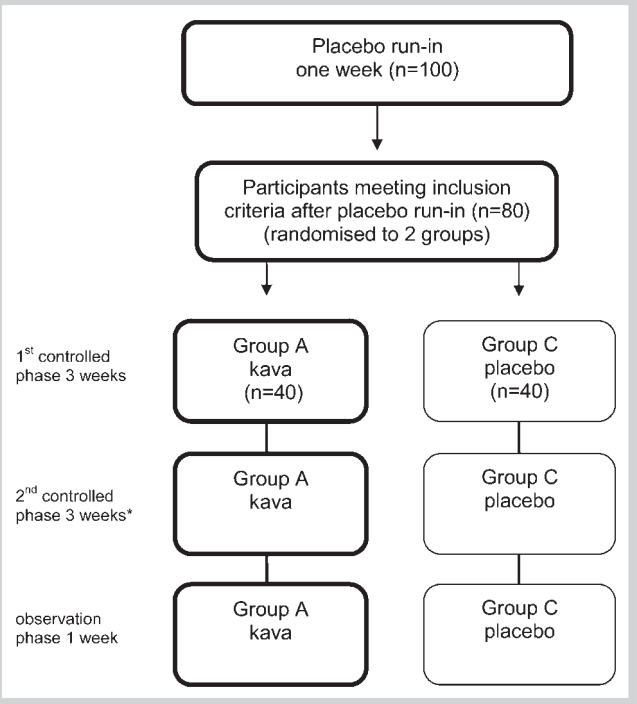

Fig. 2 Clinical trial flow chart of GAD study. * Nonresponders (< 50% reduction on HAMA) titrated from 120 mg to 240 mg of kavalactones or matching placebo.

placebo in the specific treatment of generalised anxiety disorder (GAD) is also of benefit. Previous studies comparing kava in the specific treatment of GAD are scarce. The only English language study conducted on kava versus placebo in a specific GAD sample was abandoned due to concerns of kava-induced hepatotoxicity at the time (2003–2004) [25].

The next research to address several key questions, the Kava Anxiety-Lowering Medication (KALM) project, follows from the Kava Anxiety Depression Spectrum Study (KADSS) [26]. KADSS was a 3-week placebo-controlled, double-blind, crossover trial that recruited 60 adult participants with one month or more of elevated generalised anxiety. The results revealed that the aqueous extract of kava (standardised to 250 mg of kavalactones per day) significantly reduced participants' anxiety and depression levels on the Hamilton Anxiety Scale: HAMA-F 1, 39 = 26.17, $p < 0.001$, BAI-F 1, 39 = 13.12, $p < 0.001$ (**Fig. 1**), and the Montgomery Depression Rating Scale: MADRS-F 1, 39 = 10.26, $p < 0.003$, respectively. Kava tablets used were supplied by MediHerb. Manufacture was conducted under strict pharmaceutical good manufacturing practice (Pharmaceutical GMP). The Kava (organic peeled rhizome from a noble cultivar) was sourced from Vanuatu in accordance with the Vanuatu Kava Act 2002 [27]. Tablets were formulated from pressed, dried aqueous extract and standardised to contain 50 mg of kavalactones. An independent assay using high-performance liquid chromatographic (HPLC) analysis revealed higher concentrations of the kavalactones dihydrokavain, kavain, and dihydromethysticin, moderate levels of methysticin, and lower levels of yangonin, desmethoxyyangonin, and chalcone methylesters. The extract was found to be safe and well-tolerated, with no serious adverse effects, and no clinical liver toxicity (although it should be noted that the sample size is too small to preclude the chance of liver toxicity occurring in a larger population).

The next stage of research, the KALM project, is seeking to address a gap in the research by assessing whether a traditional aqueous extract of kava (the identical extract used in KADSS: see above) is efficacious and safe in the treatment of generalised anxiety and GAD. The project comprises of 1) an acute RCT, kava (180 mg of kavalactones) versus oxazepam and placebo in 20 anxious people, testing effects on cognition (attention, memory, reaction time), mood, anxiety, and driving performance; 2) an 8-week RCT comparing kava (120 mg kavalactones) versus placebo in 100 patients with GAD. To assess differences between dosage and enhance chance of efficacy, nonresponders at 3 weeks will be titrated to 240 mg of kavalactones. The sample size required was calculated using GPower3, considering that kava versus placebo has a moderate-strong effect size (0.35) with significance (α) set at 0.05 and power (β) set at 0.80, providing critical t of 2.00. Outcomes include HAMA (primary outcome) and MADRS, the Beck Anxiety Inventory, an adverse reactions checklist, and the Arizona Sexual Experiences Scale (secondary outcomes). Other outcomes include tests of neurocognitive function and genetic tests (GABA transporter 1 and cytochrome P450 2D6 polymorphisms). Liver function blood tests will also be performed during the GAD study to check for any signs of liver inflammation (**Fig. 2**).

The primary aims of the KALM project are to 1) evaluate the efficacy of kava compared to placebo in GAD, 2) compare kava at 120 mg and 240 mg of kavalactones to determine any differences in efficacy and safety, 3) assess any side effects of kava compared to placebo, in particular any biochemical changes on liver function tests and on the Arizona Sexual Experiences Scale, 4) explore acute differences in neurocognition between a medicinal dosage of kava, oxazepam, and placebo (i.e., cognitive tests, driving, acute mood, and anxiolytic effects), 5) evaluate if non/response to kava can be correlated with genetic polymorphisms of the GABA system or cytochrome P450 enzymes.

The use of kava at an initial dose of 120 mg being titrated to 240 mg in nonresponders may determine if there is any difference in respect to safety and efficacy between the doses. While kava has been shown to be effective at both doses, it has not been confirmed whether a dose-dependent effect is present at medicinal dosage levels. The use of a sexual experiences scale to monitor potential sexual side effects from kava is likely to provide an important point of clinical difference over some conventional antidepressants, with the latter commonly producing such side effects in patients [28]. DNA microarray assays will be conducted

to explore polymorphisms for cytochrome P450 2D6 enzyme [19, 29] and GABA transporter genes (sodium and chloride dependent GABA transporter 1) [30]. This holds the potential to determine genetic profiles of responders and nonresponders who may be poor, ultra-rapid, or extensive metabolisers (as these are the genes involved with pharmacokinetic and pharmacodynamic effects) [31]. This may be due to either differing anxiolytic pharmacodynamic effects from GABA system polymorphisms or from differing serum levels of post-metabolised kavalactones by different effects of cytochrome P450 metabolism.

Future Direction of Kava

Kava's road to global re-institution is progressing and the KALM project represents a potential step forward. If the clinical trial can demonstrate safety and efficacy of an aqueous extract of the noble kava plant, this will encourage further studies, and may ease concerns about the potential reinstitution to restricted markets. Further safety studies (*in vitro, in vivo* and human) will be required in addition to a larger multicentre study (since there is currently no approval in Europe). Long-term studies are also required to assess this phytomedicine's safety and efficacy over time (including relapse rates of GAD). Currently, it remains to be seen whether kava should be used as a long-term treatment, or whether it is safer and more effective in short-term intermittent administration. To be on the side of caution, present evidence does not support long-term use of any kava products. Following the wisdom of traditional use of noble kava cultivars may provide a commonsense solution for potentially addressing concerns for hepatoxicity, while providing an efficacious medicine. An important element to the future of kava is that imports will need to meet strict quality controls, being sourced from controlled areas growing the evaluated noble kava cultivar with specific chemotypes (used for its pleasant effects with the least occurrence of side effects), and in the form of aqueous extracts of the peeled rhizome only [32]. Adequate glutathione levels in products (intrinsic or added) may also be advised to provide hepatoprotectivity. If these elements are met, a case will then be developed for the re-introduction of kava into restricted jurisdictions.

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Kava: a comprehensive review of efficacy, safety, and psychopharmacology

Jerome Sarris, Emma LaPorte, Isaac Schweitzer

Overview: Kava (*Piper methysticum*) is a South Pacific psychotropic plant medicine that has anxiolytic activity. This effect is achieved from modulation of GABA activity via alteration of lipid membrane structure and sodium channel function, monoamine oxidase B inhibition, and noradrenaline and dopamine re-uptake inhibition. Kava is available over the counter in jurisdictions such as the USA, Australia and New Zealand. Due to this, a review of efficacy, safety and clinical recommendations is advised.
Objective: To conduct a comprehensive review of kava, in respect to efficacy, psychopharmacology, and safety, and to provide clinical recommendations for use in psychiatry to treat generalized anxiety disorder (GAD).
Methods: A review was conducted using the electronic databases MEDLINE, CINAHL, PsycINFO and the Cochrane Library during mid 2010 of search terms relating to kava and GAD. A subsequent forward search was conducted of key papers using Web of Science cited reference search.
Results: The current weight of evidence supports the use of kava in treatment of anxiety with a significant result occurring in four out of six studies reviewed (mean Cohen's d = 1.1). Safety issues should however be considered. Use of traditional water soluble extracts of the rhizome (root) of appropriate kava cultivars is advised, in addition to avoidance of use with alcohol and caution with other psychotropic medications. Avoidance of high doses if driving or operating heavy machinery should be mandatory. For regular users routine liver function tests are advised.
Conclusions: While current evidence supports kava for generalized anxiety, more studies are required to assess comparative efficacy and safety (on the liver, cognition, driving, and sexual effects) versus established pharmaceutical comparators.
Key words: kava, Piper methysticum, herbal medicine, anxiety, generalized anxiety disorder.

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Kava (*Piper methysticum*) is a perennial shrub native to the ethnogeographic regions of Melanesia, Micronesia and Polynesia [1]. The name kava is derived from the Polynesian word 'awa', which is used to describe the bitter acrid taste of the psychoactive beverage prepared from the rhizome of the plant [2]. Traditionally within the South Pacific, kava extracts are prepared from masticated rhizome roots which are combined with water or

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coconut milk [3]. Kava drinking is an essential component of many Pacific Island societies. It is traditionally used during religious and cultural ceremonies to achieve an altered level of consciousness, for medicinal purposes, and at social gatherings as an inebriate beverage that elicits physiological and psychological relaxation [4]. The use of kava has been popularized since the 1990s, with dozens of kava products (of varying quality) being used worldwide for the treatment of anxiety. While selective serotonin re-uptake inhibitors (SSRIs) and benzodiazepines are effective first-line pharmacological treatments of anxiety disorders [5], side effects from both agents are common [6,7]. Thus interventions such as kava may provide another viable treatment option. Motivations for use of kava to quell anxiety maybe predicated on the belief that a natural product is safer; however, it should be noted that while complementary medicines in general are benign, not all herbal medicines are safe, nor are they all effective. While there is compelling evidence to support the use of kava in the treatment of anxiety (discussed later) [8], concerns over hepatotoxicity have led to its withdrawal or restriction in many countries since 2002 [9]. Although not currently confirmed, companies' previous use of cheap kava material (plant peelings rather than the peeled rhizome which is traditionally used), and the use of incorrect kava cultivars and chemical solvents for extraction, may be implicated in cases of liver damage [10].

While reviews have previously been conducted on kava, such as Cairney *et al*. (cf. Aust NZ J Psychiatry) [11] which explored the neurobiological effects of the plant, over recent years safety concerns have come to light, thereby a comprehensive review of kava is timely. Furthermore, kava is currently available for use over the counter in jurisdictions such as the USA, Australia, and New Zealand, thereby a review of kava's current level of efficacy, safety considerations (such as effects on the liver, cognition, and driving), and potential drug interactions are indicated, in addition to clear clinical recommendations to advise on the judicious clinical prescription of kava for anxiety.

Methods

The electronic databases Medline (PubMed), CINAHL, PsycINFO, and The Cochrane Library were accessed in mid 2010. A search was conducted using the terms *Piper methysticum*, kava, kavalactones, kavain, anxiety, generalized anxiety disorder, and GAD. A further search was conducted on the safety, pharmacokinetics and pharmacodynamics of kava, and areas pertaining to neurocognition, driving and pharmacogenomics. A forward search of key identified articles was subsequently performed using Web of Science cited reference search. Meta-analyses and randomized controlled trials (RCTs) written in English were reviewed to determine evidence of efficacy. *In vitro* and *in vivo* studies were primarily reviewed to assess pharmacodynamic and pharmacokinetic activity, and safety issues. Effect sizes were calculated in all RCTs studying kava in anxiety. From the results of the clinical trials we calculated an effect size as Cohen's d [12] by firstly subtracting the differences between the kava and placebo scores on the anxiety scale used, then dividing this by the pooled standard deviation at baseline.

Results

Pharmacology and mechanisms of action

The pharmacodynamic mechanism for kava's anxiolytic action is thought to be due to the lipophilic constituents known as kavalactones (or kavapyrones: see Figure 1) [4]. Collectively, kavalactones are concentrated mainly within the rhizomes, roots and root stems of the plant [13,14]. The distribution of kavalactones progressively decreases towards the aerial parts of the plant [14]. The aerial parts of the plant often contain toxic alkaloids such as pipermethystine, and are not used in traditional consumption [15]. Collectively, there have been identified to date 18 different kavalactones, which are typically metabolized in the liver by the cytochrome P450 system (CYP450) [16]. However, approximately 96% of the total pharmacological activity can be attributed to the presence of six kavalactones: methysticin, dihydromethysticin, kavain, dihydrokavain, demethoxyyangonin, and yangonin [14,17]. Minor constituents of kava include: amino acids, minerals (aluminium, iron, magnesium, potassium, calcium and sodium) [14] and three chalcones (flavokavins A, B and C) [18].

Several studies have documented a wide spectrum of pharmacological effects of kava including anxiolytic [19], anti-stress [19], sedative [20], analgesic [21], muscle relaxant [22], antithrombotic [23], neuroprotective [20], mild anaesthetic [24], hypnotic [25], anticonvulsant [20] actions. As detailed in Table 1, numerous *in vivo* and *in vitro* studies from animals and humans suggest possible mechanisms which may mediate the actions of kava extract and specific kavalactones including: blockade of voltage-gated sodium ion channels, reduced excitatory neurotransmitter release due to blockade of calcium ion channels, enhanced ligand binding to gamma-aminobutyric acid (GABA) type A receptors, reversible inhibition of monoamine oxidase B, and reduced neuronal reuptake of noradrenaline (norepinephrine) and dopamine. Unlike benzodiazepines, kavalactones do not bind directly to GABA, and appear to activate GABAergic effects via

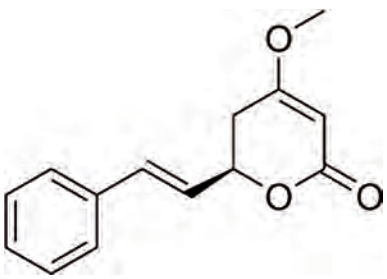

Figure 1. Kavain (major lipophilic constituent from kava).

Table 1. Kava: mechanisms of action

Mechanism of action	Study design	Key observations	Reference
Modulation of calcium and sodium channels	*In vitro* *In vivo*	Interaction of kavain with voltage-dependent sodium and calcium channels. When applied before anoxia the sodium channel blockers tetrodotoxin and kavain preserved vesicular ATP content, prevented both the veratridine-induced increases of Na^+ and Ca^{2+}	Gleitz *et al*. 1996/95 [20,68]
Voltage-dependent sodium channel inhibition	*In vitro*	Both kavain and methysticin inhibited voltage-dependent Na+ channels in acutely dissociated rat CA1 hippocampal neurons leading to a decrease of cellular excitability	Magura *et al*. 1997 [69]
Inhibition of voltage-dependent calcium channels	*In vitro*	Kavain interacted with the M3 receptor or the M3 associated G-protein receptor. The actions of kavain did not affect the prostaglandin pathways and nitric oxide mediated relaxation was not observed	Martin *et al*. 2000 [70]
Reduced neuronal re-uptake of dopamine	*In vivo*	High doses of kavain and desmethoxyyangonin increased dopamine levels in the nucleus accumbens of rats	Baum *et al*. 1998 [71]
Reduced neuronal re-uptake of noradrenaline	*In vitro*	Kavain and methysticin inhibited the uptake of noradrenaline in rat cerebral cortex and hippocampal synaptosomes	Seitz *et al*. 1997 [72]
Enhanced ligand binding to GABA-α receptors	*In vitro*	Yangonin, kavain, dihydrokavain, methysticin, and dihydromethysticin enhanced the specific binding of [3H]-bicuculline methochloride (although did not inhibit the specific binding of [3H]-flunitrazepam)	Boonen *et al*. 1998 [28]
	In vivo	Kavapyrones enhanced [3H]-muscimol binding in a concentration-dependent manner. Maximum potentiation was observed in the hippocampus, amygdala and medulla oblongata	Jussofie *et al*. 1994 [26]
Enhanced regulation of GABAergic neurotransmission	*In vitro*	Kavalactones or dihydrokavain significantly reduced the rat brain stem nucleus tractus solitarius inhibitory effects induced by muscimol	Yuan *et al*. 2002 [73]
Reversible platelet MAO-B inhibition	*In vitro*	MAO-B reversible inhibition by individual kavalactones (in order of potency): desmethoxyyangonin, methysticin, yangonin, dihydromethysticin, dihydrokavain, kavain	Uebelhack *et al*. 1998 [74]

modulation of the GABA channels, and increased binding to, and of number of, GABA binding sites [20,26]. Davies and colleagues [27] found no significant interactions between GABA or benzodiazepine binding sites and the pharmacological activities of kava within rodents; and Boonen and Häberlein [28] discovered that kavalactones dihydromethysticin, dihydrokavain, methysticin and kavain also did not bind with GABA-α receptors in an animal model (and did not antagonize flunitrazepam binding to benzodiazepine sites).

Evidence of efficacy

A Cochrane review has been undertaken of 11 RCTs of rigorous methodology using kava monopreparations (60 mg–280 mg of kavalactones) in anxiety [8]. Results revealed statistically significant anxiolytic activity of kava compared with placebo in all but one trial. A meta-analysis of seven trials using the Hamilton Anxiety Scale (HAMA) demonstrated that the plant reduced anxiety significantly over placebo, with a large effect size (see Table 2). There was moderate heterogeneity in respect to the type of extract used (acetone, ethanol, and type of standardization), dosage used (60 mg–280 mg kavalactones), and the sample treated (pre-operative anxiety, climacteric anxiety, state–trait or generalized anxiety disorder (GAD) diagnoses). The methodological quality of the trials was generally sound, with four of the seven trials including having the maximum Jadad score of five. Similar findings were also demonstrated in another meta-analysis conducted by Witte *et al*. (2005) [29], that included six placebo-controlled, randomized trials using a standardized kava extract WS1490 in non-psychotic anxiety disorders (assessed via HAMA).

In one 8-week 3-arm clinical trial (n = 129), kava demonstrated equivalent efficacy to synthetic agents, buspirone and opipramol in the treatment of GAD [30]. This demonstration of equivocal efficacy is noteworthy (although the lack of a placebo arm limits a firm conclusion) as kava may provide an advantage over synthetic comparators such as benzodiazepines, in respect to limiting daytime sedation and cognitive impairment. Preferential use of kava may potentially elicit less withdrawal and rebound problems compared to chronic benzodiazepine use.

In respect of the use of acetone and ethanol formulations of whole kava extracts in anxiety, several studies have been conducted since 1995. Six studies in English were accessible online assessing the plant for use in anxiety. Four out of the six studies revealed a positive outcome. Of the two studies with negative results on primary outcomes, a 4-week RCT by Connor and Davidson (2002: n = 37) using

Table 2. Kava: meta-analyses

First author	Methodology	Results
Pittler *et al*. 2003 [8]	Cochrane Review of 11 RCTs (N = 645) and a meta-analysis of 6 RCTs (N = 345) of kava in the treatment of anxiety	Significantly greater anxiolysis from kava than placebo; 5.0-point reduction over placebo on HAMA (95%CI: 1.1–8.8)
Witte *et al*. 2005 [29]	Meta-analysis of kava in the treatment of generalized anxiety Kava WS1490 extract 6 RCTs included	Odds ratio in favour of Kava = 3.3 (95%CI: 2.09–5.22)

HAMA, Hamilton Anxiety Scale.

a standardized extract of kava versus placebo in DSM-IV diagnosed GAD [31], revealed no difference between the treatments (d = ns). While a 4-week RCT by Gastpar and Klimm (2003) using a standardized extract of kava versus placebo in neurotic anxiety (n = 141) also revealed equivocal effects between the treatments (d = ns) on the Zung Anxiety Inventory [32]. Of the four positive studies, an RCT conducted by Geier and Konstantinowicz (2004) using a standardized kava extract (150 mg of kavalactones per day) versus placebo over 4 weeks in 50 patients with DSM-III-R non-psychotic anxiety, revealed on per-protocol analysis a significant effect in favour of kava on the HAMA (d = 0.36) [33]. A larger 25-week study by Volz *et al*. (1997) using a standardized extract of kava in 101 participants with a range of non-psychotic anxiety found superiority of the extract over placebo from week 8 onwards [34]. The effect size at week 25 between placebo and kava (in favour of treatment) was d = 0.58. A 4-week 1996 RCT (n = 58) by Lehmann and colleagues [35] using 300 mg of a standardized kava extract on general anxiety not occurring from a mental disorder revealed a significant effect in favour over placebo, and a strong effect size, d = 1.22. While slightly outside the auspices of this review, a controlled study using kava in climacteric/perimenopausal anxiety in women by Cagnacci *et al*. (2003) [36] also revealed significant results on the State Trait Anxiety Inventory (STAI) compared to control.

It should be noted that the kava formulations previously studied are no longer currently used due to being withdrawn from production after the 2002 ban of kava in the EU. In Australia the use of water soluble extracts are allowed (<250 mg of kavalactones per day) for medicinal use, and are available over the counter. Until recently however no clinical studies had been conducted to assess safety and efficacy of these formulations. An Australian study sought to address the safety concerns outlined in the World Health Organization (WHO) 2007 kava safety report [37] by using a traditional water-soluble extract of kava in the treatment of chronic anxiety. The Kava Anxiety Depression Spectrum Study (KADSS) was as a 3-week placebo-controlled, double-blind, crossover trial that recruited 60 adult participants with one month or more of elevated generalized anxiety [38]. The results revealed that the aqueous extract of kava (standardized to 250 mg of kavalactones per day) significantly reduced participants' anxiety and depression levels on HAMA with a very large effect size, d = 2.24. The aqueous extract (supplied by MediHerb) was found to be safe and well tolerated, with no serious adverse effects, and no clinical liver toxicity. The qualitative research component of the study revealed that the key themes of kava consumption were a reduction in anxiety and stress, and calming or relaxing mental effects [39]. Other themes related to improvement in sleep and in somatic anxiety symptoms. Kava use did not cause any serious adverse reactions, although a few respondents reported nausea or other gastrointestinal side-effects.

Safety

Kava was withdrawn from European and UK markets in 2002 due to concerns over reported hepatotoxicity, and to date over 100 cases of hepatotoxicity have been identified whereby kava may be implicated. In many of these case reports it was unclear whether kava was responsible for the toxic effects on the liver, particularly in those involving concomitant ingestion of other compounds with potential hepatotoxicity (e.g. other medications and/or alcohol), and in some cases a higher than recommended dose [37]. In most cases for mulations using potentized extract methods (via acetone or ethanol) were used. Factors potentially responsible for hepatotoxic effects include hepatic insufficiency to metabolize kavalactones (cytochrome P450 (CYP) 3A4, 2D6), preparations low in glutathione, and use of aerial parts or root peelings (higher in alkaloids), acetonic or ethanolic kava extraction media, or incorrect cultivar (medicinal, tudie or wichmanni varieties). Approximately 79% of individuals in a Caucasian population have shown to be deficient in CYP2D6 activity, and therefore metabolize some drugs more slowly [40], whereas the incidence of CYP2D6 deficiency in Asian populations is approximately 1%, and pure Polynesian populations have shown no deficiency of the enzyme [41]. Although the genetic polymorphism of CYP2D6 and other CYP enzymes has not yet been determined for other areas of the Pacific (e.g. Vanuatu), these studies may explain why Pacific-Asian populations have not experienced kava hepatotoxicity [42].

In response to safety concerns, the WHO commissioned a report assessing the risk of kava products [37]. Recommendation 2.1.3 suggested that products from water-based suspensions should be studied and used preferentially over acetone and ethanol extracts. This approach is supported theoretically by evidence of safety from traditional use, and aqueous extracts being rich in hepatoprotective glutathione [43]. While it seems a common sense approach to adhere to traditional usage of the plant, five cases of hepatotoxicity have been documented involving traditional water soluble extracts [44]. It is plausible that this may be due to an incorrect cultivar or plant part material (such as leaves or bark) being used, or plant substitution. Thus both the plant chemotype and the plant part used may be critical factors in hepatotoxic events.

Kava may also have a potential pharmacokinetic interaction with pharmaceutical drugs via modulation of the CYP450 system or the P-glycoprotein pump. However, although the potential of kava–drug interactions should be considered, unlike St John's wort (which has been

implicated in pharmacokinetic interactions), to our knowledge no confirmed adverse event due to pharmacokinetic interaction with pharmaceutical medicines has been documented. However, because of the inhibitory effect of kava on a range of CYP450s, potential drug toxicities may occur in preparations with narrow therapeutic windows. In respect to the hepatic pharmacokinetic modulation of CYP450s involving kava or the individual kavalactones, animal and *in vitro* models have revealed differing results. Mathews and colleagues [45] investigated the inhibition of CYP450 enzymes in human liver microsomes caused by individual kavalactones and whole kava extracts. The kava extract inhibited the activities of CYP2C9 (92%), CYP3A4 (78%), CYP1A2 (52%), CYP2D6 (73%), CYP4A9 and CYP4A11 (65%). The activities of CYP2C19, CYP2D6 and CYP2C9 were not affected. Zou and colleagues [46] also found that the most potent inhibitors of CYP450 enzymes (CYP1A2, CYP2C19, CYP3A4) were desmethoxyyangonin, dihydromethysticin and methysticin. Kavain, dihydrokavain and yangonin were not effective inhibitors [46]. Mathews *et al*. (2005) study demonstrated similar results, and additionally revealed that a whole kava extract modestly induced P-glycoprotein ATPase activity compared to control [47].

Data from these studies indicate that kava has the potential to cause herbdrug interactions via the inhibition of CYP450 enzymes which metabolize many pharmaceuticals. If kava is co-ingested with other herbal remedies, prescription medications or over-the-counter products that are metabolized by CYP450 enzymes, altered concentrations of those co-administered agents could potentially occur [42]. Common psychotropic agents that are metabolized by CYP450 enzymes include diazepam, caffeine, amitryptyline, imipramine, propranolol, fluoxetine, haloperidol, morphine, beta-blockers [42]. A single case report outlined a pharmacokinetic interaction between kava and alprazolam. A 54-year-old man had been taking both agents for 3 days prior to his hospitalization in a semi-comatose state [48]. It was postulated that kava inhibited CYP450 enzymes thereby increasing plasma alprazolam concentrations. Clear interaction, however, was not established via pharmacokinetic studies or re-challenge tests.

Heavy kava use, or abuse, has been linked to various health effects in Aboriginal communities in Australia (particularly in the Northern Territory). Frequent kava users have shown characteristics of dermopathy (dry scaling skin), increased liver enzymes gamma-glutamyl transferase and alkaline phosphatase, and lower lymphocyte counts [49]. While heavy use of kava by these communities is often consumed concomitantly with alcohol, and is a public health issue [50], this should be delineated from traditional use by Pacific Islanders in which kava is not imbibed with alcohol, having cultural significance rather than being used solely as an inebriant [1]. Furthermore, the medicinal use of kava in tablet form has a significantly lower recommended dose (average 6 gm per day), compared to daily recreational consumption as a powdered extract (average 50–200 gm per day)[38,50].

Neurocognition and driving

To our knowledge only ten clinical trials have explored the acute (n = 7) and chronic (n = 3) effects of kava on cognition. Table 3 details human RCTs which have assessed the effects of kava extract on cognition. All trials conducted used similar cognitive measures which primarily assessed facets of visual attention, memory retrieval and psychomotor function. Four out of ten studies suggest improved accuracy and performance on visual attention and working memory measures [51,54], while five out of ten studies found that kava had little or no negative effect on cognitive processes [55,59]. The remaining study revealed that kava impaired reaction time [60]. Therefore the current evidence suggests that kava has a positive or benign effect on cognition, while impairing motor skills at higher dosages.

Acute RCTs which have suggested that kava significantly enhances cognitive performance, attribute these effect to specific short-term physiological processes. For example, Thompson and colleagues [51] reported that kava improved performance in the Sperling partial report, and recognition tasks, improving the ability of selective attention, visual processing speed and increased the efficiency of memory retrieval via cues [51]. From the results it was postulated that kava decreased decay time of the presented image from iconic memory, and increased the time in which items are transferred to form a more permanent memory trace. Response accuracy was also significantly increased, indicating again that kava may have beneficial effects on working memory and retrieval processes. This study however found that reaction time was reduced by 40% in comparison to placebo, indicating a potentially negative effect on motor-skill based tasks such as driving. In addition it has also been suggested that the novel pharmacological activity of kava that distinguishes it from synthetic anxiolytics (e.g. benzodiazepines) is its ability to inhibit re-uptake of noradrenaline [54]. Research has reported that noradrenaline plays a crucial role in cognitive functions associated with the frontal lobes, and it has been implicated in a variety of cognitive processes including attention, memory formation storage and consolidation. Therefore noradrenaline may play a crucial role in the short term biochemical changes which affect cognition in short term and acute kava use.

The RCT conducted by Cairney *et al*. [60] on chronic high dose kava use, attributes significant cognitive impairment (decline in visual attention accuracy and psychomotor function) to specific brain systems associated with motor coordination and visual attention. The dose-dependent psychomotor effects of kava may reflect disruptions of GABAergically modulated functions [60]. The impaired visual attentional effects of kava resemble that of alcohol intoxication, indicating modulations to the GABA-benzodiazepine receptor complex through direct action on sodium-dependent ion channels [27].

While the current evidence on kava and cognition suggests that kava extract has a positive or benign effect on cognition (or at least no replicable deleterious effects), there are several factors which may underlie these observations. The variation of kava dosage in all RCTs should be taken into account. It is difficult to compare the psychopharmacological effects of kava across all ten studies, as each trial differs considerably in kava preparation, ingestion, quantity and potency of dosages consumed by subjects. Establishing the exact content of kavalactones consumed by subjects is also difficult as potency of kava can fluctuate according to the extraction procedure used, especially when kava is prepared in the traditional South Pacific manner [60]. Other factors include utilizing specific targeting the specific kavapyrones which may mediate the beneficial effects of kava and cognition. Most RCTs incorporated the use of whole kava extracts (which is appropriate), not assessing which individual kavalactones may be responsible for the effects on cognition or motor skills. Isolated kavalactones kavain and dihydrokavain, however, appear not to be the constituents involved with specifically modulating cognition as both isolated constituents were found to not affect learning and memory faculties [56]. Regardless, kavain and dihydrokavain may be potentially involved in modulating cognition synergistically with other constituents.

Table 3. Kava and cognition: clinical trials

Reference	Design summary	Results
Thompson *et al*., 2004 [51]	Acute: RCT n = 20 300 mg kava extract (90 mg kavapyrones) versus placebo	Kava improved the accuracy and speed of performing the SIR and SPR tasks. This reflects that kava had a superior effect on visual attention and working memory
Foo & Lemon, 1997 [55]	Acute: 3-arm RCT n = 40 1 g/kg body weight of kava versus 0.75 g/kg body weight of alcohol versus placebo	Kava alone had no effect on cognition. When kava was co-ingested with alcohol it impaired performance particularly on divided attention related tasks
Prescott *et al*. 1993 [56]	Acute: RCT n = 24 450 mg/L of kawain and dihydrokawain versus placebo	Kava reduced performance on divided attention task, increased the extent of body sway, reaction time on Sternberg memory task and other reaction time tasks. However results were not significant
Cairney *et al.* 2003 [60]	Chronic: RCT n = 28 205 g kava powder (kava users versus regular kava users (control)	Chronic kava users showed a decline in accuracy of visual attention under high load. Basic psychomotor functions (e.g. reaction time) and demanding memory tasks (e.g. paired associate learning) showed no performance deficits in chronic kava users
Russell *et al*. 1987[57]	Acute: RCT n = 10 30 g kava powder (low dose) versus 1 g/kg body weight (high dose) versus non-kava users (control)	No significant effects on any cognition domain
Saletu *et al*. 1989 [52]	Acute: 3-arm RCT n = 15 200, 400 & 600 mg of synthetic kava versus 30 g clobazam versus placebo	Kava improved intellectual performance, attention, concentration, and reaction time on 3 levels of dosage
Cairney *et al*. 2003 [59]	Chronic: RCT n = 101 current kava users (used kava for more than 6 months) versus ex-kava users (not used kava for 6 months) versus non-kava users (control)	No difference in cognitive performance between groups on all cognitive domains (motor function task, visual search, pattern recognition, pattern-location associate learning)
Heinz *et al*. 1994 [53]	Acute: 3-arm RCT n = 12 600 mg/day WS1490 kava versus 90 mg oxazepam versus placebo	Results showed kava was associated with a greater posterior N1, posterior contralateral N2 and occipital P3. Kava enhanced the allocation of attention and processing capacity. Oxazepam showed deficits in automatic feature registration, allocation of attention and available processing capacity
Mathews *et al*. 1988 [58]	Chronic: RCT n = 73 kava users (100-440 g/week of kava powder) versus non-kava users (control)	No differences in memory, cognition and coordination related to kava usage or age (picture recognition, card sorting, maze and line tracing)
Münte *et al*. 1993 [54]	Acute: 3-arm RCT n = 12 600 mg/day WS1490 kava versus 90 mg oxazepam versus placebo	Results showed that kava slightly increased word recognition rate. A larger difference was evident between old and new words. Oxazepam reduced recognition rate for both old and new words

Acute,studies which used one dose of kava and explored acute effects; Chronic, study observed effects on long-term kava users RCT, randomized controlled trial; SIR, Sternberg item recognition task; SPR, Sperling partial report.

To our knowledge only one study has assessed the potential effects of kava on driving ability. Herberg [61] conducted a randomized, double-blind, placebo-controlled trial which investigated the effects of 300 mg of kava daily over 15 days on driving ability. Participants were subjected to a battery of tests including measures of concentration, vigilance, optical orientation, motor co-ordination and reaction time under stress. Results showed that kava had no effect on measures of driving performance. Further research is needed to replicate these results and establish the acute and chronic cognitive/driving effects of kava, as it is a crucial component of the plant's risk to benefit ratio.

In summary, the current evidence overall suggests that kava extract has a positive or benign effect on cognition [51,54], or at least no replicable deleterious effects [55,59]. Despite the evidence indicating that kava can potentially enhance performance on cognitive tasks (e.g. visual processing and working memory), it is noteworthy to mention that reaction time and motor skills are significantly reduced [60]. Thus, caution is advised when driving or operating heavy machinery as psychomotor function can be signifcantly impaired when kava is consumed at higher doses. This should be considered when recommending or consuming kava therapeutically.

Clinical considerations

Prescriptive advice for clinicians regarding the use of kava to treat anxiety involves many potential considerations. Firstly, as in the case of all herbal medicinal products, quality is an important issue, as this potentially affects efficacy and safety. As current evidence suggests that previous use of cheaper kava extracts using incorrect extraction

methods, plant parts and cultivars may be implicated in hepatotoxicity, using traditional water soluble rhizome extracts of a noble cultivar of the plant is advised. Pharmaceutical grade manufacturing processes are also strongly recommended. In respect to the potential application of kava, currently the evidence supports use in chronic generalized anxiety (not GAD), as opposed to use in specific anxiety disorders such as obsessive-compulsive disorder or post-traumatic stress disorder. While one study ([34]: n = 107) demonstrated effective and safe use of kava up to 25 weeks in treatment of anxiety, longer term studies >12 months have not established safety and efficacy. As in the case of benzodiazepines, the anxiolytic action of kava has a rapid onset, thus may be more applicable for intermittent use where acute anxiolysis is required. Due to the plant having a similar clinical profile to benzodiazepines in respect to alacrity of onset (without the neurocognitive effects) monitoring for addiction or abuse is advised. It should be noted however that addiction to medicinal (low) doses of kava has not been revealed in the literature. A consideration for long-term use (or in cases of mild liver dysfunction) is to recommend routine liver function tests and hepatobiliary clinical examination. Finally, kava should not be used with alcohol or benzodiazepines, and caution should apply if the patient is taking any medication metabolized by CYP3A4 or 2D6 pathways.

Discussion

As detailed in the above review, kava is a medicinal plant that has profound psycho-neurological effects, and in the case of any psychotropic intervention, has the potential for negative consequences. While the antecedent of liver toxicity has not currently been confirmed, the use of traditional aqueous extracts from a peeled rhizome from a 'noble' chemotype of *Piper methysticum* (e.g. Borogu, used for its pleasant effects with the least occurrence of side effects) appears to be advised. Even so, additional safety data is required to assess the efficacy and safety of these extracts. Ultimately, for kava to be re-established as a safe and effective anxiolytic, a comparison is required of the plant versus both placebo and a 'gold-standard' pharmacotherapy (e.g. venlafaxine or paroxetine) in the treatment of GAD. In addition, a randomized controlled trial comparing different dosages (e.g. 120 mg 240 mg of kavalactones) on safety and efficacy outcomes should also be conducted. Previous studies comparing kava with synthetic comparators in treating GAD are limited, with the only published completed study involving a randomized, double-blind trial of kava, buspirone and opipramol [30]. As detailed above, the results of this study revealed equivalent clinical efficacy between kava and the pharmaceutical agents. However, to date no completed trial has directly compared kava to modern SSRIs, which are an accepted first-line treatment of GAD [62], although it should be noted that another previous study which compared kava to venlafaxine (a SNRI) and placebo was abandoned due to concerns of kava-induced hepatotoxicity at the time (2003 – 2004)[63].

Future research needs to determine whether a traditional aqueous extract of kava is as efficacious and safe as an SSRI in the treatment of GAD. An assessment should focus on the level and type of side effects compared to an SSRI or placebo (in particular any biochemical changes on liver function tests, and on a sexual dysfunction scale); acute differences in neurocognition between interventions, and investigate whether non-response to kava can be correlated with genetic polymorphisms of the GABA system or cytochrome P450 enzymes. While kava has been shown to be effective at various doses, it has not been confirmed whether a dose-dependent effect is present at medicinal dosage levels. The use of a sexual dysfunction scale to monitor potential sexual side effects from either kava or an SSRI is likely to provide an important point of clinical difference, with the latter commonly producing such side effects in patients [64]. Genetic tests exploring polymorphisms for CYP450 enzymes (in particular 2D6) [43,65], and GABA channel and transporter genes [66], holds the potential to determine genetic profiles of responders and non-responders [67]. This may be due to either differing anxiolytic pharmacodynamic effects from GABA system polymorphisms, or from differing serum levels of post-metabolized kavalactones by varying effects of CYP450 metabolism.

Long-term studies are also required to assess this plant medicine's safety and efficacy over time (including relapse rates of GAD). Currently it remains to be seen whether kava should be used as a long-term treatment, or whether it is safer and more effective in short-term intermittent administration. Furthermore, while traditional and clinical trial evidence has not revealed kava to be addictive, this needs to be properly evaluated. To be on the side of caution, present evidence does not support long-term use of any kava products. An important element to the future of kava is that imports will need to meet strict quality controls, being sourced from controlled areas, growing specific noble chemotypes, and must use aqueous extracts of the rhizome only. Adequate glutathione levels in products (intrinsic or added) may also be advised to provide hepatoprotectivity. While these elements may provide for a safe, effective kava formulation, as detailed above, until more safety data is accumulated, clinicians are advised to be mindful of potential interactions with medications and alcohol, and effects on the liver (thus advising occasional liver function tests), while monitoring for cases of kava misuse. Kava is an effective option to treat chronic generalized anxiety; however, as it stands more research is required to firmly support its safe prescription in mainstream psychiatry.

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[redacted]

2.3.1 Adrenaline - submission 1 of 4.

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601
Email: SMP@health.gov.au
Facsimile: 02 6289 2500

1st September, 2011

Dear Sir/Madam,

Re: Proposal to include adrenaline autoinjectors on Appendix H

[redacted] supports the need for accurate, evidence based education of all in the community regarding adrenaline autoinjectors and their use however, we do have some concerns about the proposal to include adrenaline autoinjectors on Appendix H. Whilst there is some merit in pharmaceutical companies having the ability to communicate directly with individuals such as pharmacy assistants and those working in a medical practice we do have concerns about pharmaceutical companies communicating with the general public where there is no health professional such as a pharmacist or a doctor on location.

Awareness of allergy and anaphylaxis has improved in the general community yet we continue to struggle with dissemination of accurate information on allergy and the risk of anaphylaxis. Those educating the general community must be those who have a comprehensive understanding of daily management, recognition of an allergic reaction and indeed, emergency treatment including use of the adrenaline autoinjector. In view of these concerns, [redacted] does not support the proposal to amend Appendix H to include adrenaline autoinjectors.

Our concerns surrounding the proposal include:

1. Direct consumer promotion can result in individuals purchasing an adrenaline autoinjector over the counter at a pharmacy when they do not require one. There is still limited understanding of anaphylaxis within the community and it is not unreasonable for individuals to purchase an adrenaline autoinjector for themselves or their child without medical confirmation that they require an adrenaline autoinjector.

2. The product information for adrenaline autoinjectors differs to the Australasian Society of Clinical Immunology and Allergy (ASCIA) prescribing guidelines. Individuals encouraged to purchase an adrenaline autoinjector over the counter may purchase the wrong dose device and not have the required documentation (Action Plan for Anaphylaxis which is an individualised emergency response plan outlining this information) signed by their doctor. ASCIA also does not recommend adrenaline atuoinjectors for children under 1 year of age unless specifically prescribed by an immunology/allergy specialist based on the infant's clinical history. Direct consumer promotion can

[redacted]

lead to the purchase of an adrenaline autoinjector over the counter with no/incorrect education on how to avoid an allergic reactions and therefore more importantly, when and how to use the device. When an individual is prescribed an adrenaline autoinjector by a medical practitioner, there is the opportunity to educate about avoidance strategies, when and how to use the device and the provision of an ASCIA Action Plan for Anaphylaxis. Without the knowledge of when to use the device, inappropriate use or lack of use when necessary is likely. Further to this, if the device needs to be used in an anaphylaxis emergency, but the individual has not been shown how to use it, the device may be activated inappropriately.

3. There is confusion within the community about allergy and risk of anaphylaxis and it is essential that individuals with allergy symptoms are appropriately diagnosed by an immunology/allergy specialist. If direct consumer promotion of adrenaline autoinjectors is allowed, it may result in individuals purchasing a device rather than seeking medical confirmation of risk of anaphylaxis, information on daily management and then emergency treatment.

4. Direct consumer promotion can lead to the presentation of biased information by the pharmaceutical companies promoting the device.

Thank you for affording [redacted] the opportunity to provide a submission on the said proposal.

[redacted]

[redacted]

[redacted]

2 September 2011

2.3.1 Adrenaline - submission 2 of 4.

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601
Email: SMP@health.gov.au
Facsimile: 02 6289 2500

Dear Sir or Madam,

RE: Amendment to Appendix H to include adrenaline auto-injectors

The proposal to include adrenaline auto-injectors in Appendix H is not supported by [redacted]

[redacted] does not support the proposal to include adrenaline auto-injectors in Appendix H for the following reasons:

The risks and benefits of the use of a substance

- Direct consumer promotion of adrenaline auto-injectors is medically inappropriate. Since adrenaline auto-injectors can already be purchased over the counter without prescription, patients still have the opportunity to purchase a device for clinical use if they deem it essential. Direct consumer promotion however, increases the risk of inappropriate purchase without medical advice and thus potentially alters the risk/benefit ratio.

The purposes for which a substance is to be used and the extent of use of a substance

- Adrenaline auto-injectors are used to treat potentially life-threatening anaphylaxis. [redacted] has developed prescribing guidelines for adrenaline auto-injectors to assist with the determination of level of risk of anaphylaxis and therefore the requirement for an adrenaline auto-injector. This determination requires assessment by appropriately trained medical professionals. Direct consumer promotion may result in the purchase of adrenaline auto-injectors by patients who do not normally require these devices. Examples might include individuals with a family history of anaphylaxis, allergy or asthma, but no personal history of anaphylaxis or generalised allergic reactions. Furthermore, the purchase of adrenaline auto-injectors which are not considered to be medically indicated may result in upwards pressure on PBS costs by demands by patients for renewal using PBS authority subsidized prescriptions.

[redacted]

The dosage, formulation, labelling, packaging and presentation of a substance

- The dose recommendations on the product information leaflet differs to that recommended by [redacted]. [redacted] dose recommendations are based on consensus and standard practice by [redacted] and published in the Australian Medicines Handbook and the National Prescribing Service information on adrenaline auto-injectors. Direct consumer promotion to consumers may result in confusion in terms of which dose device (0.15mg or 0.30mg) is appropriate. In addition, [redacted] dose recommendations do not support adrenaline auto-injector provision to infants unless determined as necessary by a clinical immunology/allergy specialist.

Other matters that the Secretary considers necessary to protect public health

- If consumers are encouraged to purchase an adrenaline auto-injector over the counter through direct consumer promotion, the opportunity for patient education regarding avoidance of anaphylactic triggers and training in how to use the device appropriately is lost. Knowing when and how to use the device and what to do after administration is essential. While pharmacists play a role in patient education, medical advice and training of patients is an essential part of anaphylaxis management. This is even more important with two very different devices available on the market.

- Direct consumer promotion by companies may favour one product over another and will therefore present a biased viewpoint to individuals who are not medically trained.

- [redacted] is developing e-training programs to increase community awareness of anaphylaxis. [redacted] has worked closely with the national patient organisations Anaphylaxis Australia and Allergy New Zealand and state governments to develop high quality anaphylaxis training and resources. [redacted] e-training programs for schools and childcare have educated over 11,500 individuals since it was launched in March 2010 and it is the preferred anaphylaxis e-training course in NSW, WA and QLD and the only anaphylaxis management training available in some regions in Australia.

  [redacted] is in the process of adapting the [redacted] anaphylaxis e-training for schools and childcare into an [redacted] anaphylaxis e-training course for the community, which will address first aid issues and will be targeted at the general public. Commercial promotion of adrenaline auto-injectors to consumers has the potential to undermine the educational programmes developed resulting in greater confusion and potential purchase of adrenaline auto-injectors by patients who are at minimal or no risk of anaphylaxis.

Thank you for the opportunity to provide a submission regarding this important issue.

Kind regards,

[redacted]

[redacted]

7 September 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling

– Meeting of 19 October 2011

Proposal

2.1 Adrenaline – seeking advice on a proposal to include adrenaline in Appendix H

[redacted] does not support the proposal to include adrenaline in Appendix H of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

[redacted]

[redacted]

Background

While acknowledging that responsible advertising of Schedule 3 (S3) products may have some public benefit by raising consumer awareness of relevant health conditions and prompting health professional intervention, [redacted] continues to have concerns about consumers requesting products based on an advertisement.

With S3 medicines, it is the pharmacist's responsibility to assess that the product is safe and suitable for the intended patient. This can be difficult when the customer has made up their mind and believes that they know best because of the limited, sometimes exaggerated information provided in a clever advertisement. For this reason [redacted] has been reticent to support including S3 medicines in Appendix H.

Adrenalin auto-injectors are S3 medicines available in two strengths of 300mcg/0.3ml and 150mcg/0.3ml. They are indicated[1] for the emergency treatment of anaphylaxis (acute allergic reactions) due to insect stings, drugs or other allergens. The 300mcg auto-injector is used for adults and children of 30kg or more while the 150mcg strength is used for children less than 30kg.

There are two registered auto-injector products on the market, Epipen and Anapen. Both products are listed on the Pharmaceutical Benefits Scheme (PBS) as an authority item for eligible patients for anticipated emergency treatment of acute allergic reactions with anaphylaxis that has been initially assessed by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician.

While easy to use, training/counselling is necessary so that people understand how to use an auto-injector. Information and training for the Epipen® brand of auto-injector is available online at www.epiclub.com.au, and for the Anapen® brand of autoinjector at www.anapen.com.au.

Key Points

1. Patients who would benefit from having access to adrenaline auto-injectors are best identified through health care professional intervention rather than by advertising campaigns.
2. In the event that adrenalin was included in appendix H:
    a. Pharmacists would benefit from support materials for triaging requests in order to filter inappropriate requests and ensure legitimate users are under medical supervision.
    b. Clarification is recommended regarding direct-to-consumer advertising of a medicine subsidised under the PBS.

Comments

[redacted] has considered the proposal to list adrenaline within Appendix H of the SUSMP. While [redacted] perceives some merit in raising public awareness of the

[1] Epipen Full Product Information; www.mimsonline.com.au

[redacted]

availability of adrenaline auto-injectors for the treatment of acute severe allergic reactions, we also have a number of concerns.

1. **Evidence of advertising need**
   Considering the PBS restrictions for adrenaline auto-injectors, it is reasonable to expect auto-injectors to be initiated by a specialist in accordance with PBS requirements. Supply as a valid authority PBS prescription item would generally be the most cost-effective means of access for a patient. Prescribers and pharmacists are well placed to identify patients at particular risk of anaphylactic reactions for referral to a specialist.

   [redacted] understands that restricted promotion of adrenaline auto-injectors occurs in New Zealand through consumer support groups for relevant conditions such as asthma. While there may be benefits to having limited promotion such as this, Appendix H does not include such restrictions and it would therefore be possible for sponsors to initiate more extensive campaigns.

2. **Risk of inappropriate product requests**
   [redacted] is concerned that direct to consumer advertising may prompt people with non-anaphylactic allergies to seek an adrenaline auto-injector. Consumers have a poor understanding of allergies, as demonstrated when health professionals question them on medicine allergies. It is not uncommon for a consumer to advise that they have a drug allergy when in fact it is a drug sensitivity or an adverse drug reaction.

   [redacted] is concerned that strategic advertising could promote an adrenaline auto-injector in such a way that pharmacists will need to spend significant time and effort in assessing the appropriateness of the request. For pharmacists to effectively meet their professional obligations there would need to be adequate support tools to assist them in effectively triaging requests for an auto-injector in order to filter inappropriate requests and to ensure legitimate users are under medical supervision.

   We question whether advertising would succeed in identifying a greater number of patients who would benefit from having access to adrenaline auto-injectors for emergency use or whether it would more likely prompt inappropriate requests.

3. **Advertising PBS items**
   It may not be appropriate for a medicine subsidised under the PBS to be advertised directly to consumers. We suggest this is clarified prior to any decision being made.

Conclusion

[redacted] does not consider there is a need for direct-to-consumer advertising of adrenaline auto-injectors and does not support the proposal for inclusion in Appendix H.

[redacted]

[redacted]

2 September 2011

2.3.1 Adrenaline - submission 4 of 4.

The Secretary Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601
Email: SMP@health.gov.au
Facsimile: 02 6289 2500

Dear Sir or Madam,

RE: Amendment to Appendix H to include adrenaline auto-injectors

As a specialist working in the area of allergy, I support the availability of wider awareness of the appropriate use of these devices that I understand is what is being sought under Appendix H.

There is obviously qualification to this - I would not support direct consume promotion – however it would be beneficial if training materials can be created for awareness of these in places such as public event areas, workplaces and school. Allergies are increasing in Australia and death from severe allergy is more likely to occur with failure to provide early and appropriate care. There is a limitation of access to experts in Australia for appropriate training in anaphylaxis and the proposed amendment may help in this regard.

Thank you for your consideration of my comments.

[redacted]

[redacted]

2.4 Multiple matters - submission 1 of 2.

[redacted]

SUBMISSION TO THE OCTOBER 2011 MEETING OF THE ADVISORY COMMITTEE ON MEDICINES SCHEDULING

PURPOSE

1. [redacted] makes this submission in relation to items referred by the Delegate to the October 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS) for scheduling advice.

RECOMMENDATIONS

2. [redacted] provides the following recommendations to the ACMS:

   a. **Adrenaline.** [redacted] supports the proposal to list adrenaline in Appendix H in order to facilitate awareness, education and training of consumers and carers.

   b. **Azelastine.** [redacted] supports the proposal to reschedule azelastine from Schedule 3 (S3) to Schedule 2 (S2) when supplied in topical eye preparations containing 0.05 per cent or less.

   c. **Diclofenac.** [redacted] does not support the proposal to exempt from scheduling topical preparations containing diclofenac, other than those indicated for the treatment of solar keratosis. [redacted] also seeks additional information on the rationale for the suggested alternative approaches.

   d. **Famciclovir.** [redacted] supports the proposal to reschedule 1500 mg or less of famciclovir from Schedule 4 (S4) to S3 when in oral preparations for the single dose treatment of *herpes labialis* (cold sores) in immunocompetent patients. However, [redacted] does not support the inclusion of famciclovir in Appendix H.

ADRENALINE

3. [redacted] is aware that a proposal to include adrenaline in Appendix H has previously been considered by the Committee.

4. Given the purpose of use of adrenaline auto-injector preparations (ie. emergency treatment of acute severe allergic reactions), [redacted] believes permitting direct communication with consumers is likely to assist in:

   a. raising broader awareness regarding the need for, and availability of, such treatment so that members of the public have a better understanding if they encounter such emergencies;

   b. developing education and training which is uniform across organisations and locations;

   c. delivering up-to-date education which can be tailored for the device and the audience (eg. potential users, range of carers who are not healthcare practitioners, and health professionals); and

   d. making education and training accessible on a regular basis (rather than a one-off or ad hoc exercise) so that potential users, carers and health professionals are better prepared and more confident in managing highly stressful emergency situations.

5. [redacted] aware that concerns have been expressed by some stakeholders about the need to allow brand advertising in order to facilitate education and training of consumers

and carers. [redacted] appreciates the reasons given by these stakeholders, for example, that many carers are highly educated about issues relating to acute anaphylactic reactions and that general education (independent of brand) can be provided without Appendix H listing. On balance, however, we believe the inclusion of adrenaline in Appendix H has the potential to deliver benefits overall as outlined above.

6. In addition, [redacted] notes that the rationale behind a previous request for Appendix H listing focused on the ability to deliver education and training to non-healthcare professionals. While clearly Appendix H listing brings with it the ability to advertise by brand, [redacted] also believes the risk of misuse or inappropriate requests as a result of brand advertising to be very low.

7. We would certainly be keen to ensure messages to consumers are conveyed in a manner that highlights the exact purpose of use of the preparations and that they do not inadvertently send confused or unintended messages. We are confident this would be managed through the application of the Therapeutic Goods Advertising Code.

8. In summary, [redacted] supports the proposal to list adrenaline in Appendix H in order to facilitate awareness, education and training of consumers and carers.

AZELASTINE

9. Azelastine is included in S3 when in topical eye preparations containing 0.05 per cent or less. It is also included in Appendix H.

10. [redacted] believes azelastine meets the scheduling factors listed for S2 in the *Scheduling Policy Framework for Medicines and Chemicals*. [redacted] is also aware that a number of ocular antiallergic products are currently available in S2.

11. [redacted] therefore supports the proposal to reschedule azelastine from S3 to S2 when supplied in topical eye preparations containing 0.05 per cent or less.

DICLOFENAC

12. Diclofenac in preparations for dermal use (excluding treatments for solar keratosis) containing 1 per cent or less is currently exempt from scheduling. From the pre-meeting notice [redacted] understands the applicant is seeking to extend this exemption to include topical preparations of diclofenac of all strengths (excluding treatments for solar keratosis). In addition, the two “alternative approaches” in the notice offer the possibility of retaining an upper limit (albeit higher) to the concentration for exemption from scheduling.

13. [redacted] notes that in addition to the possibility of higher strengths of diclofenac preparations being exempted from scheduling, the proposal could also result in an expanded range of products being exempted as it refers to “topical” (rather than “dermal”) preparations. We seek the release of further information to enable [redacted] to provide an informed position regarding the proposal.

14. With the level of detail provided in the pre-meeting notice, [redacted] does not support the proposal to exempt from scheduling topical preparations containing diclofenac, other than those indicated for the treatment of solar keratosis.

FAMCICLOVIR

15. [redacted] notes a proposal to reschedule famciclovir from S4 to S3 was considered in February 2009 (including Appendix H listing) and October 2009, and rejected on both occasions.

16. [redacted] is also aware that in New Zealand the distribution of famciclovir as a Restricted Medicine (equivalent to S3 here) has recently been approved.

17. [redacted] believes it is appropriate to include famciclovir in S3 in the treatment of cold sores as proposed. However, we also believe it is paramount that the applicant supports the development of a protocol and relevant materials for pharmacists by [redacted]. The protocol can appropriately address a range of issues, including those raised previously by stakeholders and Committee Members, for example:

a. comparative efficacy between single-dose oral therapy, single-day multi-dose oral therapy, topical therapy and placebo;

b. that treatment must be initiated promptly for optimal effectiveness (and therefore appropriate access through the S3 pathway can provide benefits);

c. appropriate screening processes (eg. impaired renal function);

d. prevention of off-label use through appropriate screening and referral processes;

e. suggested frequency of use (eg. for repeated requests); and

f. likelihood or otherwise of the development of resistance through increased use in the community.

18. In summary, [redacted] supports the proposal to reschedule 1500 mg or less of famciclovir from S4 to S3 in oral preparations for the single dose treatment of *herpes labialis* (cold sores) in immunocompetent patients. [redacted], however, does not support Appendix H listing given the lack of local (Australian) data of famciclovir as a non-prescription medicine.

Submitted by:

[redacted]

[redacted]

2.4 Multiple matters - submission 2 of 2.

To Whom it may concern

RE: Notice inviting public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990

The following submission is presented on behalf of the [redacted]

In June to August 2011, Western Australia responded to the rapidly emerging availability and use of synthetic cannabinoids by scheduling 21 synthetic cannabinoids as Schedule 9 substances under the Western Australia *Poisons Act 1964*. This action effectively banned the possession, sale or supply of these substances in Western Australia. An initial group of 7 synthetic cannabinoids were listed as schedule 9 substances on 17 June 2011. A second group of 14 substances were scheduled on 5 August.

The Western Australian Government's Drug and Alcohol Office has established an interagency Government group to coordinate action and provide advice to Government about synthetic cannabinoids and other synthetic substances that may emerge. The Group is titled the Western Australian Synthetic Substance Review Group. It's membership includes the:

- Western Australian Drug and Alcohol Office
- Western Australian Police
- Western Australian Department of Health – Pharmaceutical Services Branch
- Western Australian ChemCentre
- Western Australian Department of Commerce – Consumer Protection

In response to the Notice inviting public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990, [redacted] supports the following proposed amendments:

2.7 3,4-Methylenedioxypyrovalerone (MDPV) - seeking advice on a proposal to include 3,4-methylenedioxypyrovalerone in Schedule 9 with a cross-reference from the common name MDPV to 3,4-methylenedioxypyrovalerone.

2.9 Synthetic cannabinoids - the delegate is seeking advice on the appropriate scheduling of the following synthetic cannabinoids and classes of synthetic cannabinoids, in particular inclusion in Schedule 8 or 9 with the possibility of cut-offs to unscheduled for lower concentrations:

- Dibenzopyrans
- Cyclohexylphenols

[redacted]

- Naphthoylindoles
- Naphthylmethylindoles
- Naphthoylpyrroles
- Naphthylmethylindenes
- Phenylacetylindoles
- Benzoylindoles

The delegate is seeking advice on the potential unintended regulatory impact of this type of decision. The delegate is also seeking advice on alternate wording of the schedule entry to possibly refer to:

- 'synthetic agonists of cannabinoid receptors or synthetic cannabinomimetics'; and/or
- 'substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols'.

In relation to the proposed amendment 2.7 regarding 3,4-Methylenedioxypyrovalerone (MDPV), [redacted] would support the inclusion of MDPV into Schedule 9 as it is appearing in samples submitted to ChemCentre. There are documented examples in the international literature of harm caused by use of this drug. It also appears to have no medicinal value.

In relation to the proposed amendment 2.9 regarding synthetic cannabinoids, [redacted] is supportive of including the listed synthetic cannabinoids and classes of synthetic cannabinoids in Schedule 8 or 9. [redacted] supports a precautionary approach towards new substances with the potential to cause harm. Synthetic cannabinoids do not appear to have any legitimate therapeutic use and the potential psychological and physiological harms of consuming these substances are unknown. There are recorded and anecdotal examples received by [redacted] that support users experiencing harms that associate with using synthetic cannabinoid products.

[redacted] consider that the scheduling of the 8 classes of synthetic cannabinoids would be the most comprehensive way of dealing with the scheduling. If there are any useful compounds that are inadvertently caught in the scheduling they can be dealt with on a case-by-case basis. The inclusion of these groups, especially into Schedule 9, is appropriate due to the potential, or in some cases proven, harmful nature of these compounds without any therapeutic value.

It is also the view of [redacted] that the alternative wording clause should not be used as it will prove difficult to categorically designate compounds based on the receptor they act on, or that they have pharmacologically similar action to THC, particularly as they are essentially research chemicals that have not been comprehensively studied and it makes the scheduling unnecessarily burdensome to administer.

The delegate may wish to consider requiring manufacturers, distributors and retailers to prove that any new product containing a synthetic cannabinoid not captured in the eight classes of synthetic cannabinoids proposed for

scheduling is safe for consumption and does not pose any reasonable risk of harm.

From an operational perspective, the scheduling of the 8 classes of synthetic cannabinoids would simplify processes for Police if "synthetic cannabinoid" was a distinct drug category. [redacted] will also consider recommending necessary amendments to the Western Australian *Misuse of Drugs Act 1981* to reflect new substances in the Poisons Standard (the SUSMP) and the Western Australian *Poisons Act 1964*.

Removing synthetic cannabinoids from legal sale and possession is expected to result in a significant decrease in consumption and the associated harm related to its use. One of the indicators that [redacted] has been monitoring is the proportion of positive tests being detected by the ChemCentre. They receive samples from a range of employers across Western Australia and across different industries, including mining, transport and various industry contractors.

The ChemCentre has recently provided information regarding trends in testing which has shown declines in use from a peak prior to 17 June (first group of synthetic cannabinoids listed as Schedule 9 substances in WA) of 16.3% positive tests to 2.1% in the week following the 2nd group of 14 substances that were scheduled on 5 August 2011.

I trust that this submission is of assistance to the Committee in its considerations of the proposed amendments as outlined in the TGA delegate's notice paper.

[redacted]