Complementary Medicines Australia submission to the public Therapeutic Goods Administration Consultation: Changes to permissible ingredients - Low-negligible risk.

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Introduction

CMA is committed to a vital and sustainable complementary medicines sector supporting domestic skilled jobs, research, manufacturing and exports. CMA members include stakeholders across the value chain – including manufacturers, raw material suppliers, distributors, consultants, retailers and allied health professionals.

Complementary Medicines Australia (CMA) welcomes the opportunity to make a submission in relation to proposed changes to the 26BB Permissible Ingredients Determination.

Length and relevance of warning statements

As a general statement relevant to all current and future consultations, we note that the proposed warning statements are excessively and unnecessarily lengthy. Very lengthy warning statements have always been strongly opposed due to pragmatic label space considerations particularly since the introduction of the TGO 92 that further introduces label space limitations.

The select consumer groups that represent the genuine views of everyday Australians often report that the lengthier warning statements become, they become increasingly less likely they are to be read, comprehended, or taken seriously by the consumer.

In addition, proposed warning statements are not taking into account the intended purpose of medicines for relevance. This should be considered carefully so as to avoid redundant or unnecessary regulation and avoid the need for future changes to the requirements.

Boron

Internal use

CMA notes the alignment of the TGA's dosage recommendations on boron in children with that of the European Medicines Agency who have established the following limits on daily dosage:

- <2 years - 1 mg boron/day
- <12 years - 3 mg boron/day
- <18 years - 7 mg boron/day
- ≥18 years - 10 mg boron/day

Although the principles are not opposed, the approach to implementing the principles requires improved alignment to real world use of boron generally, to listed medicines, and existing product warnings applied to listed and registered medicines.

The consultation proposal is:
When the maximum recommended daily dose of the medicine provides more than 3 mg of boron and the medicine is for internal use and/or oral application, the following warning statement is required on the label:

- (BORON12) 'Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future.'.

When the maximum recommended daily dose of the medicine provides more than 1 mg of boron but less than 3 mg of boron and the medicine is for internal use and/or oral application, the following warning statement is required on the label:

- (BORON2) 'Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.'

The wording of the statement above by the EMA is written in this way as it is intended for application to boron as an excipient.

A large proportion of the medicines on the ARTG that contain boron are medicines that are for an older adult population, including calcium formulas, glucosamine formulas, and multivitamins for adults or older adults, and are accordingly presented as large tablets or capsules. The above warnings are entirely redundant for these classes of medicines that would never be given to younger children, and these large dosage forms could never be accidentally swallowed or used by children.

The proposed statements are not consistent with the longstanding TGA approach to warning statements, which is to remain succinct and avoid raising undue fear and distress, even where the link is well established in humans, let alone where the link is based only animal studies or other secondary sources of evidence:

Short Description
Adults only. OR Not to be used in children under two years of age
Adults only. OR Not to be used in children under two years of age
Caffeine is not recommended for children.
Children, pregnant or breastfeeding women, and those who have recently had a heart...
Do not use... in children 6 years of age or less.
If diarrhoea persists for more than 6 hours in infants under 6 months, 12 hours in children under 3.
Keep out of reach of children
May be dangerous, particularly to children if used in large amounts
Not suitable for children
Not suitable for use in children under the age of 12 months, except on health professional advice.
Products containing activated charcoal should be used with caution in children since it may...
Use in children under 12 years is not recommended
Use in children under 12 years is not recommended. AND If symptoms persist, seek the...
Use in children under 3 years is not recommended
Use in children under 9 years is not recommended.

For the above reasons, CMA provides that the proposal requires amendment to:

- Remove both proposed requirements and replace with:
  - **When the maximum recommended daily dose of the medicine provides more than 1 mg of boron, the following warning statement is required on the label: 'Not to be used in children' or 'Not to be used in children under 12' (at sponsor discretion).**
- Should only be applied to dosage forms that are accessible to children under 12, including liquids, powders, chewable tablets, pastilles.
- We do not agree with the application of lengthy warning statements describing particular issues in children for medicines that are not indicated for children.

In regards to the specific reference to the boron fertility theory, listed medicines are an insignificant risk as they are produced in controlled GMP facilities with extremely conservative quantities of boron (relative to the nutrient reference values). There is a far larger risk to children from large boron exposure via common household routes, therefore any corresponding advice from a public health perspective is therefore far more appropriate through Government advisory websites for consumers. Sources other than TGA medicines include:

- The common trend to use borax in making slime or putty with young children.
- Use of powdered pure borax as a pesticide, as a household cleaner on floors and kitchen surfaces, as a laundry washing aid, as a pesticide in vegetable gardens, or even as a 'folk remedy' style anti-microbial or skin healing dietary* addition (*not from TGA listed medicines).

Therefore it is far more relevant and appropriate for the Department of Health to provide general public health information about reducing children's total exposure to boron through household, recreational, or other off-label unapproved means, than a warning statement on labels for low dose and GMP controlled medicines that are unlikely to be indicated for use in children.

External use - boron

When the medicine is for topical use for dermal application, the following warning statement is required on the label:

- (EXTRNL) 'For external use on unbroken skin only.' (label warning or directions for use).

The term 'For external' is redundant when the requirement is that it is applicable for topical use. In the principle of keeping warnings short and relevant, **'Use on unbroken skin only'** is sufficient.

Withania somnifera

The consultation proposes the label claim:

'Consult a health care professional prior to use if you are pregnant or breastfeeding.'

Pregnancy

ACCM provided that there is insufficient anecdotal and clinical evidence to establish that *Withania somnifera* is either safe in pregnancy or is used as an abortifacient.

The rationale for this proposal is based on seven traditional texts and ethnobotanical surveys.

Five references suggest that its use to aid conception, pregnancy and lactation, to treat infertility and menstrual irregularities.

Two references suggest from limited size ethnobotanical surveys that *Withania somnifera* may have been used for abortifacient action, although it is not clear whether this is used in respect of viable pregnancy or non-viable pregnancy. Other herbs, but not Withania, mentioned in the in the surveys refer specifically to "anti-fertility" actions rather than abortifacient information alone. Herbs that have uterine tonic actions are used in traditional herbal medicines for a variety of female complaints requiring female tonicity, including menorrheal complaints, post-partum uterine tonicity and health, etc. Without access to safe surgical methods to treat non-viable pregnancy, uterine tonic herbs were also used in high doses to aid evacuation of non-viable pregnancies. This contextual consideration of herbal traditions should be considered when reviewing traditional/ ethnobotanical information for herbs.

Regarding the evidence:

1. The evidence selected for review is primarily tradition in nature, at the exclusion of the typically applicable experimental models used to establish risk to maternal and foetal health, such as animal toxicity studies;
2. Of the evidence published in the consultation, the majority suggested that Withania is safe in pregnancy and lactation;
3. The book by Sahu (1982) is very limited in relevant information;
4. Mahmood is narrative on the diversity of medicinal plants used in the Gujrawala District in Pakistan and does not discuss toxicity;
5. Moteetee (2016) is a study an ethnobotanical survey of hundreds of plants in an area. It does not describe the interview methods or the search method performed. It concludes that 87 plants were used for several reproductive problems, and lists WS as one example for removing contents of conception, which suggests any abortifacient use is used only for

traditional treatment of non-viable pregnancy and for the removal of placenta post-partum, whereas it is also used to induce pregnancy as a uterine tonic. It does not weight WS as more dangerous than any of the other plants mentioned in the survey.

6. The following 2015 toxicity study was not included in the evidence, which[1] delivered rats delivered 3g/kg/day of WS extract during organogenesis and histogenesis and observed no evidence of foetal toxicity, or maternal toxicity. The paper concludes that 'Withania somnifera extract caused no changes in the body weight of parental females, number of corpora lutea, implantations, viable foetuses, external, skeletal and visceral malformations".
7. The 2018 review by Azgomi on female and make reproductive health found positive effects on both reproductive systems. The search strategy included *in vivo* and *in vitro* models and included pregnancy in the search terms. No negative findings regarding pregnancy were reported.
8. The studies cited in relation to abortifacient activity would not satisfy the TGA's evidence guideline requirements for traditional evidence, which says that "to substantiate the use, action or indication of an ingredient with traditional based evidence, the TGA Evidence Guidelines require documented evidence that the medicine has been used for at least 75years in the tradition to which it belongs." The evidence guidelines go on to state that 'this will establish that it belongs to that tradition and that there is an accumulated repository of observations in humans that underpins the use of the medicine.' Whilst this discussion is not about an indication, it still relates to a proposed physiological action of Withania. As traditional use is the majority of the evidence cited to support this concern, the CMA suggested that the evidence listed does not sufficiently establish and associated observations of the medicine in a single tradition of medicine.
9. Many couples and women are prescribed Withania during fertility treatment by healthcare practitioners at typical doses, an indication which is supported by the traditional information available.
10. The references to the mouse study refer to the use of a "very high" dose. Although the traditional information is extremely scant, other Ayurvedic references also suggest that normal doses have no effect and are safe compared to very high doses:
"*Large dosage of WS is abortifacient (Ability to cause abortion). The normal dosage is generally safe and we use it in India along with other herbs even during pregnancy*."[2]

The evidence cited in support of the proposed concerns about Withania are inadequate to apply to all listed medicines containing this ingredient, and not supported by available data. *Withania somnifera* is a commonly used herb for women of child bearing age. Herbalists in Australia and around the world have commonly used *Withania somnifera* at standard doses as a supportive tonic for stress and other conditions, including female health, for decades. The herbal practitioner community have not developed any particular concerns with Withania in respect to pregnancy over this time at usual dosages, similarly, the Database of Adverse Event Notifications (DAEN) does not include any gynaecological reactions despite widespread use in listed medicines for women of childbearing age.

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1 Prabu 2015. Prenatal developmental toxicity evaluation of Withania somnifera root extract in Wistar rats. Drug Chem Toxicol. 2015 Jan;38(1):50-6. doi: 10.3109/01480545.2014.900073

2 "UTILIZATION OF ASHWAGANDHA (WITHANIA SOMNIFERA) ROOT POWDER IN FORMULATION OF HEALTH FOODS" (2007) https://pdfs.semanticscholar.org/e12c/05f9d21c4890afb745e8ee278ad1d6733115.pdf

Label warning statements regarding pregnancy and lactation are being recommended with greater frequency for listed medicine ingredients. Whilst CMA appreciates due caution be applied in these groups, in this instance, the label warning statement appears to contradict the traditional indications for use mentioned in the literature that support use for fertility and pregnancy, particularly at standard doses.

In regards to the proposed wording, it's quite possible they could be taking Withania before they know they are pregnant. Consultation 'prior to' would not be possible and may results in undue distress in pregnancy women, which is not appropriate considering there is limited evidence relating to pregnancy and that which is available refers to "very" high doses.

Lactation

There is no evidence of any kind to suggest that *Withania somnifera* has any adverse effects on women or babies during lactation. There is no known toxic compounds identified for Withania that would suggest there would be any concern of transference to breast milk. Withania in general is recognised as a widely studied, widely used herb without toxicity issues. There is evidence that Withania has been safely used for long periods of time, including Ayurvedic use, as a galactogogue (helps to induce milk supply) and as a uterine tonic to help with post-partum recovery. In short, a warning statement in lactation is not only not supported, such a warning is strongly contradicted by available information and traditional use.

Summary:

- There is extremely limited evidence that *Withania somnifera* has any adverse effect upon pregnancy. Withania is a herb that has been very widely used by herbalists for women for decades and has been used widely in listed herbal medicines for many years indicated for stress in women. Despite this lengthy and widespread use in Australia, no concerns with pregnancy have arisen at usual doses. There are no gynaecological events on the DAEN database.
- The limited evidence based on the study in mice is reported to only have occurred in very high doses, and the limited traditional information also suggests that any such action is also in relation to very high doses, although it is not clear whether it is used for viable pregnancies or only for non-viable pregnancy. Other than the limited suggestion around very high doses. Therefore the evidence available, although limited, is quite clear that there is a dose-dependent relationship that is based on "very" high doses, whereas other use is recognised as safe and even indicated in pregnancy at normal dosages. Therefore it is clearly not applicable to apply a pregnancy warning to medicines that do not include very high dosages of Withania, of which there are many on the ARTG.
- The proposed term 'prior to' would induce unwarranted distress if a woman becomes pregnant unexpectedly.
- There is no provided evidence to contradict use in lactation. Conversely, there is a long history of use as a breast milk stimulant and a post partum uterine tonic. There doesn't appear to be any valid justification for requiring a warning for lactation.

Vitex agnus-castus

Proposed label claim: *'Vitex agnus-castus can affect hormones in the body and may interact with prescription medicines such as oral contraceptives. Consult your health care professional before use*.'

The TGA substantiates the proposed warning statement with the following evidence, of which only one item is considered to be primary evidence.

Health Canada. (2018, 03/06/2019). Chaste Tree - Vitex Agnus-Castus. Retrieved from http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=chaste.tree.vitex&lang=eng

European Medicines Agency. (2017). *Final European Union herbal monograph on Vitex agnus-castus L., fructus.* (EMA/HMPC/606742/2017). London UK: European Union Retrieved from https://www.ema.europa.eu/en/medicines/herbal/agni-casti-fructus

World Health Organization. (2009). *Who Monographs on Selected Medicinal Plants.* In WHO Consultation on Selected Medicinal Plants, Vol. 4. (pp. 24). Retrieved from https://www.medbox.org/traditional-treatment/who-monographs-on-selected-medicinal-plants-volume-4/preview

National Center for Complementary and Integrative Health. (2016, 29/11/2016). Chasteberry. Retrieved from https://nccih.nih.gov/health/chasteberry

Bone, K., & Mills, S. (2005). *The Essential Guide to Herbal Safety* (First ed.). (pp. 333-336) Edinburgh: Elsevier Churchill Livingstone.

Liu, J., Burdette, J. E., Xu, H., Gu, C., van Breemen, R. B., Bhat, K. P. L., Booth, N., Constantinou, A. I., Pezzuto, J. M., Fong, H. H. S., Farnsworth, N. R., Bolton, J. L. (2001). Evaluation of Estrogenic Activity of Plant Extracts for the Potential Treatment of Menopausal Symptoms. *Journal of Agricultural and Food Chemistry, 49(5)*, 2472-2479. doi:10.1021/jf0014157

Regarding the evidence:

1. The Health Canada monograph contains a similar suggested warning statement, with all references for this statement being secondary and published at 2000, 2006 and 2010. No primary resources citing known mechanisms of action or actual adverse reactions regarding the oral contraceptive pill are used on the monograph to support the warning statement.

2. The EMA monograph of 2010 and which, was revised and adopted again in 2018, states no known adverse reactions under section 4.5, but also states *"Because of the possible dopaminergic and oestrogenic effects of agnus castus fruit interactions with dopamine agonists, dopamine antagonists, oestrogens and antioestrogens cannot be excluded."* Yet under 5.1 Pharmacological effects, the same monograph says that the action is unknown.

   The EMA monograph does not include miscarriage or any other pregnancy complications under 4.8 Undesirable effects sub-heading.

3. The referenced NIH monograph warns against the use of Vitex alongside the oral contraceptive pill amongst other hormonal treatments but provides no reference for this remark.

4. The reference that 'the impact of *Vitex agnus-castus* on estrogen and progesterone metabolism is also scientifically recognised; isn't supported by the reference (6) which refers to a wide number of herbs and their use in treating menopause, rather than effecting hormonal regulation to the extent that OCPs are effected. The relevance of the statement and the reference to the proposal is not clear.

The evidence does not include a 2006 systematic review of the safety of Vitex[3] which also reports on adverse international adverse event data, and finds no unplanned pregnancies or interactions with women on the OCP.

The single reported adverse event regarding the progestogen only pill, commonly known as the "mini pill" is not conclusive or information as this pill is reported to have a failure rate of 9% under typical circumstances.

Vitex agnus-castus has been used widely and popularly in female fertility treatment, and normalising menstrual cycles. As noted on the TGA website it may be used at the same time as the oral contraceptive pill. However the available evidence does not document any effects on these medications.

The proposed label warning statement is not supportable given the evidence to support it is limited and theoretical at best.

Consultation Proposals

The consultations are presented almost as if they are pre-determined, which appears as an inflexible approach, rather than following recommended Government guidelines, for example, presenting 4 different regulatory options. We support the application of BPR for all TGA consultations relating to listed medicines.

3 Daniele C et al. Vitex Agnus Castus: A systematic Review of Adverse Events. Drug Safety 2005; 28 (4): 319-332