SUBMISSION

RESPONSE TO THE *PROPOSED CHANGES TO REQUIREMENTS FOR LISTED MEDICINE INGREDIENTS: ANNUAL LOW-NEGLIGIBLE RISK CHANGES 2021-2022*

ITEM 4: ARTEMISININ AND PREGNANCY RISK

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Prepared by: Rose Cornelissen, Jenny Carè and Tristan Carter, on behalf of the Naturopaths & Herbalists Association of Australia (NHAA)

Naturopaths & Herbalists Association of Australia
ABN 25 000 009 932
Founded 1920

3/2-4 Holden St
Ashfield NSW 2131
Australia

PO Box 696
Ashfield NSW 1800
Australia

Phone: +61 2 9797 2244
Email: nhaa@nhaa.org.au
Web: www.nhaa.org.au

1. BACKGROUND

1.1 ABOUT THE NHAA

The NHAA is the peak professional association for the naturopathy and Western herbal medicine professions in Australia. Established in 1920, it is also the oldest professional association of complementary therapists in the country. The NHAA represents around 2,000 practitioners and is a member of the World Naturopathic Federation (WNF) which represents practitioners globally.

Our members provide primary care services to people suffering both acute and chronic conditions. We use a combination of therapies, including diet, exercise, stress management, supplementation and herbal medicine formulations to deliver holistic treatments. We work alongside other health professionals to support conventional treatment and play an important role in public health, including the safe use of medicines by Australian consumers.

The primary aims of the NHAA is to:

- Promote, protect and encourage the learning, knowledge and service delivery of naturopathic and Western herbal medicine
- Disseminate such knowledge through available media and networks
- Encourage the highest ideals of professional and ethical standards
- Promote naturopathic and Western herbal medicine as safe and effective public healthcare
- Engage with legislative tools and their representatives as they relate to the practice of naturopathic and Western herbal medicine in Australia

The vision of the NHAA is:

- Practitioners and the practice of naturopathic medicine and Western Herbal medicine are fully integrated into the primary healthcare system in Australia
- The NHAA is recognised as the peak body for naturopathic and Western Herbal medicine
- Naturopathic and Western Herbal medicine is accessible to all
- The integrity of the profession of naturopathic and Western Herbal medicine is maintained
- The standards and quality of education of the professions continue to be promoted
- Career opportunities and research pathways for naturopathic and Western Herbal medicine professionals are developed and maintained
- The integration of traditional knowledge and evolving science is continued

The NHAA publishes the quarterly *Australian Journal of Herbal & Naturopathic Medicine (AJHNM)*. The AJHNM publishes material on all aspects of medical herbalism and naturopathic practice including philosophy, phytochemistry, pharmacology, clinical applications and research. The NHAA also holds annual seminars throughout Australia, with the Herbal and Naturopathic International Conference held biennially. Since its inception, the NHAA and its members have been at the forefront of naturopathic and Western Herbal medicine and have been influential in areas ranging from education and practice to ethical, regulatory and industry standards.

2. RESPONSE TO THE PROPOSED CHANGES TO REQUIREMENTS FOR LISTED MEDICINE INGREDIENTS ITEM 4: ARTEMISININ AND PREGNANCY RISK

2.1 TGA PROPOSAL AND RATIONALE

The TGA proposes the inclusion of a warning statement on the medicine label advising consumers to avoid use during pregnancy for ingredients that contain artemisinin for *A. dracunculus, A. frigida, A. pallens, A. vulgaris* and davana oil (derived from *A. pallens*).

Pregnancy safety advice for *Artemisia* species was issued in October 2020 based on a systematic review (González et al., 2020) which demonstrated artemisinin and its derivatives to be embryotoxic in animals. As a result, the condition of listing for products containing *A. annua* or *A. absinthium* to include a label warning against use of the product during pregnancy was issued.

The TGA is currently proposing that a warning statement also be applied to the remaining *Artemisia* species on the Permissible Ingredients Determination (as listed above). Although these *Artemisia* species contain lower amounts of artemisinin and present a lower risk during pregnancy, the TGA considers their safety for use in pregnancy has not been established.

2.2 NHAA ASSESSMENT AND COMMENTS

2.2.1 Appropriate engagement with the evidence of safety for herbal products

As with pharmaceuticals, there are ethical challenges associated with the conduct of clinical trials in populations of pregnant women. As such, safety data is largely based on animal studies and observational epidemiological research. Added to this, reviewing isolates in herbal products present limitations for transferability due to confounders such as natural herbal phytochemical interactivity and complexity, its effect on bioavailability in humans, and dosage. Most research examining the safety of herbal preparations in pregnancy is more appropriately represented by epidemiological research as a result. If animal studies are necessary, use of the whole herb would provide a more representative model.

2.2.2 Review of the evidence used as a basis for the proposal

The evidence originally selected for review by the TGA (Gonzalez et al., 2020) was based on animal toxicity assessments. Of the studies examined, the majority used isolated artemisinin derivatives. Therefore, making an informed assessment for the proposed labelling of certain *Artemisia* species was difficult to reconcile. Only two studies in the review met the representative criteria for assessment of *Artemisia* species. One study (Boreto et al., 2008) used artemisinin from *A. annua* with 7 mg/kg/day on gestational days 7-13 producing no change compared to controls. However, 35 or 70 mg/kg/day produce high foetal loss.

The second study (Abolaji et al., 2013) involved the plant *A. annua* with an artemisinin yield of 1.098%. Doses of 100 and 200 mg/kg/day of the herb on gestational days 8-19 produced no observed malformations, however, at 300 mg/kg/day nonviability and malformation was observed (21% and 31% respectively). It was concluded that dosing outside the normal therapeutic range using a high artemisinin containing plant required caution in pregnancy.

The above animal studies suggest low artemisinin-based interventions from a herbal source is low risk, however the NHAA acknowledges that professional prescribing and supervision is required, and further research is needed.

Finally, the Gonzalez et al. (2020) systematic review raised a significant limitation and suggested further investigation into the apparent reduced sensitivity to artemisinins found in human pregnancy.

2.2.2 Adding a 2020 review of the safety of artemisinin derivatives in the first trimester of pregnancy

The NHAA would like to draw attention to a 2020 review which included human data for assessing the safety of artemisinin combination therapy (ACT) in the 1st trimester of pregnancy for the treatment of uncomplicated malaria (D'Alessandro et al., 2020). The review assessed data from 15 observational and comparative studies for ACT from 1998 to 2020. Despite preclinical research on administration of artemisinin derivatives showing embryotoxicity, the authors noted that "Clinical data on the safety profile of ACT in pregnant women have not shown an increased risk of miscarriage, stillbirth, or congenital malformation, nor low birth weight, associated with exposure to artemisinins in the first trimester." The authors acknowledged the lack of clinical trials due to ethical concerns was problematic, but the available human studies provided invaluable human pregnancy data.

2.2.3 World Health Organization (WHO) recommendations

The WHO initially recommended that due to limited safety data, artemisinin compounds should not be used in the 1s trimester, and only be used in the 2nd and 3rd trimester of pregnancy when other treatments for malaria were considered unsuitable. However, endorsement for the use of ACT in the 1st trimester was given by the Malaria Policy Advisory Committee of WHO in 2015 (WHO, 2015), but is yet to be implemented (WHO, 2019). This was noted by Gonzalez et al., 2020 who cautioned against changes to the guidelines for use in 1st trimester until further risk-benefit analysis has been undertaken.

2.2.4 Prescribing in a professional setting

Professionally trained naturopaths and Western herbalists with degree-qualifications use products 'for practitioner dispensing only' and are educated to not prescribe the use of artemisinin containing herbs such as *Artemisia annua* in pregnancy. A label warning confirms the established evidence-based prescribing behaviour of naturopaths and Western herbalists in Australia. Despite the evidence that low artemisinin containing products are

unlikely to be embryotoxic, a level of caution is recommended. Unlike products for practitioner dispensing only, we recommend that retail products containing artemisinin which can be self-selected by an unqualified person, requires a safety warning.

We would therefore like to highlight the need to consider differentiating between professional prescription and public self-selection.

2.4 NHAA CONCLUSION

Based on the lack of definitive human safety data required by the TGA on the intake of artemisinin from certain *Artemisia* species in the 1st trimester of pregnancy, and applying the precautionary principle for this vulnerable population group, the NHAA supports the addition of a warning statement on the medicine label "Do not use if pregnant or likely to become pregnant". We would also like to highlight the following points:

- Advice pertaining to herbal products be based on robust, expertly informed and relevant research evidence.
- That the risks associated with products prescribed by health professionals are differentiated from products available for self-selection in a retail setting.

The NHAA appreciates the opportunity to contribute to the review of the proposed safety guidelines and in doing so, continue to support the health and wellbeing of pregnant women and their children in Australia.

References

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