Australian Government
Department of Health
Therapeutic Goods Administration

# Proposed changes to requirements for listed medicine ingredients: Annual low-negligible risk changes 2021-2022

## Consultation paper

Version 1.0, August 2021

TGA Health Safety Regulation

**Confidentiality**
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

# Contents

# Introduction

The Therapeutic Goods (Permissible Ingredients) Determination ('the Determination') is a legislative instrument under section 26BB of the Therapeutic Goods Act 1989. This instrument specifies all of the ingredients that are available for use in listed and assessed listed medicines and their associated requirements. The Determination is continually reviewed by the TGA to ensure that all ingredients and their requirements are appropriate for use in low-risk medicines.

## Purpose

The proposed ingredient changes in this consultation have been reviewed and categorised as being of low-negligible risk. The purpose of this consultation is to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes, which are proposed to commence on **1 March 2022** (see schedule for low-negligible risk changes for 2021-2022). Sponsors will be provided with a 12-month transition period from the commencement of the Determination to align their products with these changes.

## Transition expectations

Transition periods provide sponsors of existing listed medicines with time to make the necessary arrangements to bring their products into compliance. Sponsors should ensure that no product is **released for supply** after the expiry of the transition period, unless that product (including the details in the Australian Register of Therapeutic Goods (ARTG) listing) is compliant with any new applicable requirements.

After the expiry of the transition period, any ARTG listings or product **released for supply** that does not comply with the new requirements may be targeted for review.

# Proposed changes to requirements for listed medicine ingredients

## 1. Allergen statement for mollusc-derived ingredients

### Background

Clear labelling of allergens that may be present in a food or a therapeutic good promotes the safety of consumers who are allergic to those substances. Food Standards Australia New Zealand (FSANZ) announced an update to their Plain English Allergen Labelling requirements in December 2020 to include an allergen warning statement for food derived from molluscs, and clarified that molluscs are distinct from the definition of 'fish' in the Australia New Zealand Food Standards Code – Standard 1.1.2 (Food Standards Australia New Zealand, 2020).

FSANZ has identified three marine mollusc classes (bivalves, gastropods, and cephalopods) as being implicated in cases of food allergy (Food Standards Australia New Zealand, 2018). The FSANZ safety assessment concluded that mollusc allergy is of clinical significance in Australia and New Zealand, and that cross-reactivity between molluscs and crustacea is likely to be relatively low, meaning individuals who are allergic only to one of these foods can usually tolerate the other (Food Standards Australia New Zealand, 2020). It is expected that medicines that contain these allergens would also carry the same risk of allergy as in a food context.

Labelling requirements for fish and crustacean products are already specified in the Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92); however, there is currently no requirement for products containing mollusc or mollusc products.

The TGA proposes that ingredients on the Permissible Ingredients Determination that are derived from a marine mollusc (specifically of the bivalve, gastropod, or cephalopod class) be updated to include the warning statement "Contains mollusc" or "Contains mollusc products", similar to what is required for foods. This will promote the safety of at-risk consumers by increasing consistency in allergen labelling across food and medicine.

Currently, the Permissible Ingredients Determination requires listed medicines that contain the ingredients 'squid oil' or 'concentrated squid omega-3 triglycerides' to carry the warning statement "Contains seafood" on the medicine label. This statement is not specific and may indicate to consumers that the medicine contains either fish, crustacea or mollusc. It is proposed that this warning statement requirement is also replaced with the "Contains mollusc" or "Contains mollusc products" warning statement below.

### Consultation

The TGA is seeking consultation on an amendment to the requirements of the ingredients below included in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to address the risk of allergic reactions from ingredients derived from mollusc.

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredients below will have until the end of the transition period to amend their products in line with any new specific requirements.

### Affected ingredients

- CONCENTRATED SQUID OMEGA-3 TRIGLYCERIDES
- GREEN LIPPED MUSSEL
- GREEN LIPPED MUSSEL DRIED
- GREEN LIPPED MUSSEL OIL
- OYSTER
- OYSTER SHELL
- SEPIA
- SQUID OIL

As of the 12th July 2021, there were 115 listed medicines included in the ARTG that contained at least one mollusc-derived ingredient.

## Proposed specific requirements

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| CONCENTRATED SQUID OMEGA-3 TRIGLYCERIDES | Only for oral use.<br>'Concentrated squid omega-3-triglycerides' must be obtained from species of the order Teuthida of the class Cephalopoda AND be in combination with other ingredients in the preparation AND be presented in a therapeutic dosage form for therapeutic use.<br>The medicine requires the following warning statement on the medicine label:<br>- (SFOOD) 'Derived from seafood'. | Only for oral use.<br>'Concentrated squid omega-3-triglycerides' must be obtained from species of the order Teuthida of the class Cephalopoda AND be in combination with other ingredients in the preparation AND be presented in a therapeutic dosage form for therapeutic use.<br>~~The medicine requires the following warning statement on the medicine label:~~<br>~~- (SFOOD) 'Derived from seafood'.~~<br>The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| GREEN LIPPED MUSSEL | | The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| GREEN LIPPED MUSSEL DRIED | | The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| GREEN LIPPED MUSSEL OIL | | The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| OYSTER | | The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| OYSTER SHELL | | The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| SEPIA | Only for use as an active homoeopathic ingredient. | Only for use as an active homoeopathic ingredient.<br><br>The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |
| SQUID OIL | Only for use in oral medicines.<br><br>The medicine requires the following warning statement on the medicine label:<br>- (SFOOD) 'Derived from seafood'.<br><br>Must be obtained from species of the order Teuthida of the class Cephalopoda, be used in combination with other ingredients in the medicine and be presented in a therapeutic dosage form for therapeutic use. | Only for use in oral medicines.<br><br>~~The medicine requires the following warning statement on the medicine label:~~<br>~~- (SFOOD) 'Derived from seafood'.~~<br><br>Must be obtained from species of the order Teuthida of the class Cephalopoda, be used in combination with other ingredients in the medicine and be presented in a therapeutic dosage form for therapeutic use.<br><br>The following warning statement is required on the medicine label:<br>- (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.' |

# 2. Peripheral neuropathy associated with lower dose vitamin B6

## Background

Vitamin B6 is a water-soluble, essential nutrient found in food. Vitamin B6 represents six separate chemical entities: pyridoxine (or pyridoxol), pyridoxal, pyridoxamine, and their phosphate derivatives (National Health and Medical Research Council, 2006). Pyridoxine hydrochloride, pyridoxal 5-phosphate, and pyridoxal 5-phosphate monohydrate are available for use in listed medicines. Pyridoxine can also exist as a naturally occurring glucoside form that is converted to active forms within the human body.

Currently, the use of vitamin B6 in listed medicines is limited to a maximum of 200 mg of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose and preparations that contain more than 50 mg are required to carry a warning statement alerting consumers to the risk of peripheral neuropathy.

The consumption of vitamin B6 has been referred to as a possible cause of peripheral neuropathy (Scott et al., 2008). Accumulation of vitamin B6 through supplemental intake can cause certain adverse effects such as drowsiness, tingling, burning, or numbness (Expert Group on Vitamins and Minerals, 2003). Doses of vitamin B6 greater than 600 mg/day can lead to more severe temporary nerve impairment (Phillips et al., 1978).

In May 2020, the TGA issued a web statement to warn consumers and healthcare professionals of the potential for peripheral neuropathy from products containing less than 50 mg pyridoxine and from polypharmacy of vitamin B6-containing products.

### *International regulation*

The regulatory approach for acceptable levels and warnings varies internationally.

The European Food Safety Authority report on tolerable upper intake levels for vitamins and minerals established a daily upper limit for supplemental pyridoxine of 25 mg/day, following consideration of a clinical study undertaken over a 2-3 year period (European Food Safety Authority, 2006).

The U.S. Food and Drugs Administration and Health Canada set an upper safe limit of 100 mg/day derived from an assessment by the Food and Nutrition Board of the Institute of Medicine (Institute of Medicine, 1998, 2006).

The Association of Southeast Asian Nations report on the General Principles for Establishing Maximum Levels of Vitamins and Minerals in Health supplements recommends a maximum limit of 100 mg/day vitamin B6. However, Thailand has implemented its own limit of 2 mg/day (Association of South East Asian Nations, 2012).

The Expert Group on Vitamins and Minerals UK (EVM), of the Medicines and Healthcare products Regulatory Agency UK , established a safe upper limit for daily consumption of vitamin B6 based on a study of canine subjects (Expert Group on Vitamins and Minerals, 2003). The study demonstrated that doses of 50 mg/kg bw/day (3 g/day for a 60 kg human adult) caused nerve tissue damage within the 100 – 114per day study period. As part of the same study, a high dose group (200 mg/kg bw/day; 12 g/day for a 60 kg human adult) experienced greater nerve tissue damage, and within 40–75 days the subjects developed muscle weakness, loss of balance and impaired coordination (Phillips et al., 1978). The EVM concluded a safe upper limit for daily consumption corresponded to 0.17 mg/kg bw/day or 10 mg/day for a 60 kg human adult.

### *Australian context*

Between February 2004 and February 2021, the TGA received 11 adverse event reports showing a relationship between nervous system disorders and the intake of preparations providing less than 50 mg equivalent pyridoxine per day, with a report associated with taking a daily dose of 8.7mg of equivalent pyridoxine.

An additional 5 adverse event reports in this period were received noting nervous system disorders associated with taking multiple vitamin B6-containing products simultaneously (polypharmacy). Individually, products in these reports provided less than 50 mg equivalent pyridoxine and were not required to carry the existing warning statement. The TGA is also aware of reports overseas, which indicate that peripheral neuropathy may occur at a daily dose of less than 50 mg a day of vitamin B6, or in consumers taking more than one product containing vitamin B6.

There were products included in the reports described as “multivitamin” or “magnesium” which does not readily alert consumers to the presence of vitamin B6. When included as an active ingredient in a listed medicine, vitamin B6 is only required to be named as “pyridoxine hydrochloride” or “pyridoxal 5-phosphate (monohydrate)” in the list of active ingredients on the product label. This may lead to consumption of multiple products with vitamin B6 resulting in additive effects. However, consumers may not readily identify they are taking multiple sources of vitamin B6.

Indications for these products described in the reports included “support nervous system health” and “reduce muscle cramps”. Both vitamin B6 deficiency and excess may result in neuropathy (Donofrio, 2005). Without an appropriate warning statement, consumers may take more vitamin B6 rather than ceasing and seeking medical attention.

The Nutrient Reference Values for Australia and New Zealand for vitamin B6 published by the National Health and Medical Research Council (NHMRC) establish appropriate upper levels of intake of 50 mg pyridoxine per day. This upper level was derived considering data establishing a no observed affect level of 200 mg pyridoxine per day. Due to limitations of the quality of studies involving lower doses of vitamin B6, the no observed affect level was divided by a factor of 4 to account for this uncertainty. Taking into consideration metabolic body size and growth, upper levels for other ages were established (Table 1) (National Health and Medical Research Council, 2006).

*Table 1: Upper level of intake (UL) of Vitamin B6 as pyridoxine (National Health and Medical Research Council, 2006)*

| Population | UL of Vitamin B6 as pyridoxine (mg/day) |
|---|---|
| Infants (0-12 months) | N/A[1] |
| *1-3 years* | 15 |
| *4-8 years* | 20 |
| *9-13 years* | 30 |
| *14-18 years* | 40 |
| Adults (19+ years) | 50 |

The TGA sought advice from the Advisory Committee on Complementary Medicines (ACCM) on the peripheral neuropathy associated with pyridoxine at the 27th ACCM meeting in March 2021. Specifically, the TGA sought the committee's views on whether risk mitigation strategies are warranted for listed medicines that provide less than 50 mg equivalent pyridoxine per day; whether the current maximum daily dose for listed medicines (200 mg equivalent pyridoxine) is appropriate; and if there should be any specific requirements relating to vitamin B6 for paediatric populations. The committee recommended that:

- Risk mitigation measures are warranted for listed medicines that provide less than 50 mg equivalent pyridoxine per day.
- Products should carry warning labels that make specific reference to the adverse effects such as tingling and numbness, and that a healthcare practitioner should be consulted if symptoms are experienced.
- The maximum daily dose of vitamin B6 for listed medicines should be decreased to 50 mg equivalent pyridoxine per day.
- The maximum daily dose for paediatric populations should be in accordance with the age-based daily dose requirements for vitamin B6 that coincide with the current NHMRC guidelines.
- Paediatric products containing vitamin B6 should also carry warning statements as recommended.
- Education of consumers and health professionals/practitioners, and advice to sponsors on vitamin B6 is needed alongside the vitamin B6 dose changes and warning label additions.

## Consultation

The TGA proposes a reduction of the maximum supplemental daily intake from 200 mg/day to 50 mg/day to align with recommendations put forward by ACCM. This aligns with the NHMRC limits.

To address the risks of peripheral neuropathy from medicines containing doses of pyridoxine lower than 50 mg, it is proposed that the current Vitamin B6 warning statement requirement be extended to include products providing more than 10 mg of equivalent pyridoxine. This aligns

[1] Not possible to establish; source of intake should be breast milk, formula or food only.

with the recommendations put forward by the EVM and provides early advice to consumers to cease taking vitamin B6.

The TGA is seeking consultation on an amendment to the requirements of the below affected ingredients in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to address the risk of peripheral neuropathy from pyridoxine intake.

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the ingredients listed below will have until the end of the transition period to amend their products in line with any new specific requirements.

## Affected ingredients

- PYRIDOXAL 5-PHOSPHATE
- PYRIDOXAL 5-PHOSPHATE MONOHYDRATE
- PYRIDOXINE HYDROCHLORIDE

As of the 17 June 2021, there were 1270 listed medicines included in the ARTG containing the above ingredients.

## Proposed specific requirements

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| PYRIDOXAL 5-PHOSPHATE | Pyridoxine is a mandatory component of Pyridoxal 5-phosphate.<br><br>The percentage of pyridoxine from pyridoxal 5-phosphate should be calculated based on the molecular weight of pyridoxal 5-phosphate.<br><br>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.<br><br>If the medicine contains more than 50 mg and no more than 200 mg of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' | Pyridoxine is a mandatory component of Pyridoxal 5-phosphate.<br><br>The percentage of pyridoxine from pyridoxal 5-phosphate should be calculated based on the molecular weight of pyridoxal 5-phosphate.<br><br>The maximum recommended daily dose of the medicine must not provide more than:<br>(a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive);<br>(b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive);<br>(c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive);<br>(d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and<br>(e) ~~200~~ 50 mg of pyridoxine for individuals aged 19 years and older.<br><br>If the medicine contains more than ~~50~~ 10 mg ~~and no more than 200 mg~~ of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' |

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| PYRIDOXAL 5-PHOSPHATE MONOHYDRATE | Pyridoxine is a mandatory component of Pyridoxal 5-phosphate monohydrate.<br><br>The percentage of pyridoxine from pyridoxal 5-phosphate monohydrate should be calculated based on the molecular weight of pyridoxal 5-phosphate monohydrate.<br><br>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.<br><br>If the medicine contains more than 50 mg and no more than 200 mg of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' | Pyridoxine is a mandatory component of Pyridoxal 5-phosphate monohydrate.<br><br>The percentage of pyridoxine from pyridoxal 5-phosphate monohydrate should be calculated based on the molecular weight of pyridoxal 5-phosphate monohydrate.<br><br>The maximum recommended daily dose of the medicine must not provide more than:<br>(a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive);<br>(b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive);<br>(c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive);<br>(d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and<br>(e) ~~200~~ 50 mg of pyridoxine for individuals aged 19 years and older.<br><br>If the medicine contains more than ~~50~~ 10 mg ~~and no more than 200 mg~~ of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' |

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| PYRIDOXINE HYDROCHLORIDE | When not used as an active homoeopathic ingredient, pyridoxine is a mandatory component of Pyridoxine hydrochloride.<br><br>The percentage of pyridoxine from pyridoxine hydrochloride should be calculated based on the molecular weight of pyridoxine hydrochloride.<br><br>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.<br><br>If the medicine contains more than 50 mg and no more than 200 mg of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' | When not used as an active homoeopathic ingredient, pyridoxine is a mandatory component of Pyridoxine hydrochloride.<br><br>The percentage of pyridoxine from pyridoxine hydrochloride should be calculated based on the molecular weight of pyridoxine hydrochloride.<br><br>The maximum recommended daily dose of the medicine must not provide more than:<br>(a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive);<br>(b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive);<br>(c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive);<br>(d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and<br>(e) ~~200~~ 50 mg of pyridoxine for individuals aged 19 years and older.<br><br>If the medicine contains more than ~~50~~ 10 mg ~~and no more than 200 mg~~ of pyridoxine per maximum recommended daily dose the medicine requires the following warning statement on the medicine label:<br>- (VITB6SX) 'WARNING - Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible. [Contains vitamin B6].' |

# 3. Risk to infants from nasal use of benzalkonium chloride

## Background

Benzalkonium chloride as a mixture of quarternary benzyldimethylalkylammonium chlorides is a commonly used excipient in over the counter and prescription medications, specifically in eye drops and nasal sprays for its anti-bacterial properties. The Therapeutic Goods (Permissible Ingredients) Determination (No. 1) 2021 permits the use of benzalkonium chloride as an excipient only with the following specific requirements:

> Only for use in topical medicines for dermal application and nasal sprays.
> The concentration in the medicine must be no more than 5%.

Inhalation of benzalkonium chloride can cause constriction of the airways within the lungs (bronchospasm), the restriction of movement along the airway surfaces reducing effectiveness of the body's cleaning of the respiratory system, rebound nasal congestion, and white blood cell (neutrophil) dysfunction (Miszkiel et al., 1988; Bernstein, 2000; Graf et al., 1995; Håkansson et al., 1989).

These adverse effects have a greater significance in infants (<2 years) due to anatomical/physical differences, potentially initiating an asthmatic event or activating a predisposition for asthma (Miszkiel et al., 1988). Asthmatic events in infants are more likely to precipitate respiratory arrest. In addition, infants are unable to communicate symptoms of these adverse effects, therefore there is a risk of serious complications in infants following exposure. As such, the risk of bronchospasm and other respiratory issues from benzalkonium chloride in infant-directed applications in the form of nasal sprays presents a risk that is not acceptable in the low-risk frame for listed medicines.

## Consultation

The TGA is seeking consultation on an amendment to the requirements for benzalkonium chloride in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to address the risk of bronchospasm and other adverse effects associated with nasal sprays/drops that contain benzalkonium chloride targeted at infants under 2 years of age.

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the ingredients listed below will have until the end of the transition period to amend their products in line with any new specific requirements.

### Affected ingredients

- BENZALKONIUM CHLORIDE

As of the 9th July 2021, there were 6 listed medicines included in the ARTG containing benzalkonium chloride for nasal inhalation/application. There are currently two listed medicine nasal sprays containing benzalkonium chloride included on the ARTG which are specifically marketed for use in children. The TGA is aware that some of these products may already have a warning statement advising against use under 2 years of age.

## Proposed specific requirements

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| BENZALKONIUM CHLORIDE | Only for use in topical medicines for dermal application and nasal sprays.<br><br>The concentration in the medicine must be no more than 5%. | Only for use in topical medicines for dermal application and nasal sprays.<br><br>The concentration in the medicine must be no more than 5%.<br><br>When benzalkonium chloride is used in a nasal spray dosage form which is either:<br>a) indicated for use in children; or<br>b) not specifically indicated for adults only;<br>the following warning statement is required on the medicine label:<br>- (NTAKEN2) 'Not to be taken by children under 2 years old' (or words to that effect). |

# 4. Artemisinin and pregnancy risk

## Background

Artemisinin is a sesquiterpene lactone that is derived from certain *Artemisia* plant species (Numonov et al., 2019). *Artemisia annua* is known as "qing hao" in traditional Chinese medicine practice, and is used for treating "lingering heat in joints and bones" and "exhaustion due to heat/fevers" (Hsu, 2006).

A systematic review (González et al., 2020) found artemisinin and its derivatives to be embryotoxic in animals. Animal studies of *Artemisia annua* extracts, artemisinin and related compounds have shown the potential for both pregnancy loss (miscarriage) and developmental abnormalities in animals. The TGA published a safety alert in October 2020 concerning the risk of embryotoxicity associated with taking artemisinin during pregnancy.

As *A. annua* and *A. absinthium* contain higher levels of artemisinin (Numonov et al., 2019), the TGA considered products that contained these ingredients to present a high risk to consumers during pregnancy. The TGA considered that this risk could be appropriately mitigated by the inclusion of a warning statement on the medicine label advising consumers to avoid use during pregnancy.

In March 2021, the TGA recalled products containing *A. annua* or *A. absinthium* and issued a condition of listing, pursuant to section 28 of the *Therapeutic Goods Act 1989*, on each existing listed medicine for these products to include a label warning against use of the product during pregnancy. A requisite change to the Permissible Ingredients Determination to reflect the requirements from the conditions for listing is anticipated for August 2021.

Other *Artemisia* species are known to contain lower amounts of artemisinin than *A. annua* and *A. absinthium*, and products that contain these other *Artemisia* species present a lower risk of artemisinin than *A. annua* and *A. absinthium* when used during pregnancy. It is proposed that this warning statement requirement be applied to the remaining *Artemisia* species on the Permissible Ingredients Determination that have not been established to be safe in pregnancy and are known to contain artemisinin. Individuals should be alerted to the potential risks associated with use during pregnancy for ingredients that contain artemisinin being *A. dracunculus, A. frigida, A. pallens, A. vulgaris* and davana oil (derived from *A. pallens*) (Numonov et al., 2019; Suresh et al., 2011; Pellicer et al., 2018).

## Consultation

The TGA is seeking consultation on an amendment to the requirements of the ingredients below as included in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to address the pregnancy risk described above associated with the intake of artemisinin from certain *Artemisia* species.

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the ingredients listed below will have until the end of the transition period to amend their products in line with any new specific requirements.

### Affected ingredients

- ARTEMISIA DRACUNCULUS
- ARTEMISIA FRIGIDA
- ARTEMISIA PALLENS
- ARTEMISIA VULGARIS
- DAVANA OIL

As of the 2nd July 2021, there were 83 listed medicines included in the ARTG containing at least one of the above ingredients. Additionally, davana oil was identified as an ingredient in 71 proprietary ingredient flavour or fragrance formulations available for use in listed medicines.

## Proposed specific requirements

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| ARTEMISIA DRACUNCULUS | Thujone is a mandatory component of Artemisia dracunculus.<br><br>The concentration of thujone from Artemisia dracunculus in the medicine must be no more than 4%. | Thujone is a mandatory components of Artemisia dracunculus.<br><br>The concentration of thujone from Artemisia dracunculus in the medicine must be no more than 4%.<br><br>The following warning statement is required on the medicine label:<br>- (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect). |
| ARTEMISIA DRACUNCULUS | Thujone is a mandatory component of Artemisia frigida.<br><br>The concentration of thujone from Artemisia frigida in the medicine must be no more than 4%. | Thujone is a mandatory component of Artemisia frigida.<br><br>The concentration of thujone from Artemisia frigida in the medicine must be no more than 4%.<br><br>The following warning statement is required on the medicine label:<br>- (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect). |
| ARTEMISIA PALLENS | Thujone is a mandatory component of Artemisia pallens.<br><br>The concentration of thujone from Artemisia pallens in the medicine must be no more than 4%. | Thujone is a mandatory component of Artemisia pallens.<br><br>The concentration of thujone from Artemisia pallens in the medicine must be no more than 4%.<br><br>The following warning statement is required on the medicine label:<br>- (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect). |

| Ingredient name | Existing specific requirements | Proposed specific requirements |
|---|---|---|
| ARTEMISIA VULGARIS | Thujone is a mandatory component of Artemisia vulgaris.<br><br>The concentration of thujone from Artemisia vulgaris in the medicine must be no more than 4%. | Thujone is a mandatory component of Artemisia vulgaris.<br><br>The concentration of thujone from Artemisia vulgaris in the medicine must be no more than 4%.<br><br>The following warning statement is required on the medicine label:<br>- (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect). |
| DAVANA OIL | Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.<br><br>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.<br><br>If used in a fragrance the total fragrance concentration in a medicine must be no more 1%. | Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.<br><br>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.<br><br>If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.<br><br>The following warning statement is required on the medicine label:<br>- (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect). |

# Making a submission

The TGA is requesting comments that will help ensure that the proposed requirements are appropriate and support the quality and safety of listed and assessed listed medicines. To provide feedback on this consultation, please provide your submission using the file upload function on the Consultation Hub web page. You do not have to address all proposals. However, when responding, please clearly identify the proposal you are responding to.

Submissions may include any further data or information that may assist the Delegate to make an informed decision. Submissions may also include, for example, suggested improvements or an assessment of how the proposed change will affect you.

All submissions will be considered after the consultation period ends and may be published on the Consultation Hub web page with your consent.

## Privacy and your personal information

The TGA collects your personal information in this submission in order to:

- Contact you if the TGA wants to seek clarification of issues raised in your submission or to check whether you consent to certain information that you have provided being made publicly available.
- Help provide context about your submission (e.g. to determine whether you are an individual or a director of a company or representing an interest group).

The TGA may disclose your name and your designation/work title on the Consultation Hub web page (i.e. make this information publicly available) if you consent to the publication of your name. **Please do not** include personal information about other individuals in the body of your submission. Personal information in this context means information or an opinion about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion. Any text within the body of your submission that you want to remain confidential should be clearly marked 'IN CONFIDENCE' and highlighted in grey.

Please note that the TGA will not publish personal information about you/others without your/their consent unless authorised or required by law.

# Timetable

This consultation opened on **Wednesday 4 August 2021**.

Interested parties should respond by close of business **Wednesday 15 September 2021.** Please note that late submissions after this date may not be considered.

Following consideration of public submissions, outcomes of these proposals will be published to the Consultation Hub web page by **Wednesday 1 December 2021.**

The confirmed changes to the Determination will commence on **Tuesday 1 March 2022**.

The transition period of 1 year will end on **Wednesday 1 March 2023** unless otherwise specified.

# Enquiries

Please contact us if you have any questions relating to this consultation at the following email address: listed.medicines@health.gov.au.

# References

ASSOCIATION OF SOUTH EAST ASIAN NATIONS 2012. Annex X. ASEAN General Principles for Establishing Maximum Levels of Vitamins and Minerals in Health Supplements. 4.0 ed. Available from: https://asean.org/wp-content/uploads/2017/09/ASEAN-General-Principles-for-Max-Levels-Vitamins-Minerals-HS-V4.0-wi....pdf.

BERNSTEIN, I. L. 2000. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucociliary transport. *J Allergy Clin Immunol,* 105**,** 39-44.

DONOFRIO, P. D. 2005. Evaluating the Patient With Peripheral Neuropathy. *AANEM 52nd Annual Scientific Meeting.* Monterey, California: American Association of Neuromuscular & Electrodiagnostic Medicine. Available from: https://www.aanem.org/mxonline/resources/downloads/products/2005CourseA.pdf#page=33.

EUROPEAN FOOD SAFETY AUTHORITY, SCIENTIFIC PANEL ON DIETETIC PRODUCTS, NUTRITION AND ALLERGIES 2006. Tolerable Upper Intake Levels For Vitamins and Minerals. 29-44. European Food Safety Authority. Available from: https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf.

EXPERT GROUP ON VITAMINS AND MINERALS 2003. Safe Upper Levels for Vitamins and Minerals. 81-92. Medicines and Healthcare Products Regulatory Agency UK. Available from: https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf.

FOOD STANDARDS AUSTRALIA NEW ZEALAND 2018. Supporting document 1: Safety Risk assessment - Proposal P1044: Plain English Allergen Labelling. Available from: https://www.foodstandards.gov.au/code/proposals/Documents/P1044%20SD1.pdf.

FOOD STANDARDS AUSTRALIA NEW ZEALAND 2020. Approval report - Proposal P1044: Plain English Allergen Labelling. Food Standards Australia New Zealand. Available from: https://www.foodstandards.gov.au/code/proposals/Documents/P1044%20Approval%20Report.pdf.

GONZÁLEZ, R., PONS-DURAN, C., BARDAJÍ, A., LEKE, R. G. F., CLARK, R. & MENENDEZ, C. 2020. Systematic review of artemisinin embryotoxicity in animals: Implications for malaria control in human pregnancy. *Toxicol Appl Pharmacol,* 402.

GRAF, P., HALLÉN, H. & JUTO, J. E. 1995. Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers. *Clin Exp Allergy,* 25**,** 395-400.

HÅKANSSON, B., FORSGREN, A., TEGNER, H. & TOREMALM, N. G. 1989. Inhibitory effects of nasal drops components on granulocyte chemotaxis. *Pharmacol Toxicol,* 64**,** 321-323.

HSU, E. 2006. The history of qing hao in the Chinese materia medica. *Trans R Soc Trop Med Hyg,* 100**,** 505-508.

INSTITUTE OF MEDICINE 1998. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. The National Academies Press. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114310/.

INSTITUTE OF MEDICINE 2006. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. The National Academies Press.

MISZKIEL, K. A., BEASLEY, R., RAFFERTY, P. & HOLGATE, S. T. 1988. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. *Br J Clin Pharmacol,* 25**,** 157-163.

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL 2006. Nutrient Reference Values for Australia and New Zealand: Vitamin B6. 75-80. Canberra, Australia: Australian Government Department of Health and Ageing, New Zealand Ministry of Health. Available from: https://www.nhmrc.gov.au/about-us/publications/nutrient-reference-values-australia-and-new-zealand-including-recommended-dietary-intakes.

NUMONOV, S., SHAROPOV, F., SALIMOV, A., SUKHROBOV, P., ATOLIKSHOEVA, S., SAFARZODA, R., HABASI, M. & AISA, H. A. 2019. Assessment of Artemisinin Contents in Selected *Artemisia* Species from Tajikistan (Central Asia). *Medicines (Basel),* 6**,** 23.

PELLICER, J., SASLIS-LAGOUDAKIS, C. H., CARRIÓ, E., ERNST, M., GARNATJE, T., GRACE, O. M., GRAS, A., MUMBRÚ, M., VALLÈS, J., VITALES, D. & RØNSTED, N. 2018. A phylogenetic road map to antimalarial *Artemisia* species. *J Ethnopharmacol,* 225.

PHILLIPS, W. E. J., MILLS, J. H. L., CHARBONNEAU, S. M., TRYPHONAS, L., HATINA, G. V., ZAWIDZKA, Z., BRYCE, F. R. & MUNRO, I. C. 1978. Subacute toxicity of pyridoxine hydrochloride in the beagle dog. *Toxicology and Applied Pharmacology,* 44**,** 323-333.

SCOTT, K., ZERIS, S. & KOTHARI, M. J. 2008. Elevated B6 levels and peripheral neuropathies. *Electromyogr Clin Neurophysiol,* 48**,** 219-223.

SURESH, J., SINGH, A., VASAVI, A., IHSANULLAH, M. & MARY, S. 2011. Phytochemical and pharmacological properties of *Artemisia pallens*. *International Journal of Pharmaceutical Sciences and Research,* 5**,** 3081-3090.

# Version history

| Version | Description of change | Author | Effective date |
|---|---|---|---|
| V1.0 | Original publication | Complementary Medicines Evaluation Section | August 2021 |

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
**https://www.tga.gov.au**

Reference/Publication #