



Australian Government

Department of Health

Therapeutic Goods Administration

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

Final Decisions

Version 1.0, December 2021

TGA Health Safety
Regulation

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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 changes to ingredient requirements in the Determination were presented for consultation after they were reviewed and categorised as being of [low-negligible risk](#). The purpose of this consultation was to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes prior to their implementation.

This document outlines the final decisions made regarding the proposed changes to ingredient requirements specified in the Determination, in consideration of the consultation submissions received. These changes will commence on **1 March 2022** (see [schedule for low-negligible risk changes for 2021-2022](#)). Following commencement of the updated Determination, sponsors will be provided with a 12-month transition period to align their products with these changes.

Public consultation

The consultation opened on **4 August 2021** and closed on **29 September 2021**. The original closing date was extended by 10 business days to accommodate disruptions from state-wide lockdowns in Australia.

The TGA thanks all respondents for their participation in this consultation process. A total of 20 responses to the consultation were received from health professionals, professional bodies, consumer organisations, industry organisations, and medicine sponsors/brands and manufacturers.

All submissions that gave permission to be published are now available on the [Consultation Hub](#). Submissions received with claims of confidentiality or privacy have been redacted or remain unpublished as specified by the submitter.

Transition expectations

All changes proposed as a result of this consultation will commence on **1 March 2022**, and will include a 12-month transition period until **1 March 2023**.

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 listing 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

The TGA proposed specific requirements to promote the safety of at-risk consumers by increasing consistency in allergen labelling across food and medicine. Further details regarding the background of this issue and the proposed changes are included in the [Consultation Document](#) provided on the Consultation Hub.

Consultation submissions

All respondents agreed with the need to promote consumer safety through allergen labelling on medicines. One respondent recommended that the proposed warning “Contains mollusc” could instead be “Contains shellfish”, as shellfish is a more commonly recognised phrase. Another respondent noted their concern that this requirement was being implemented in the Determination instead of in Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (‘TGO 92’), leading to the fractionation of allergen statements between the two instruments.

TGA response

The proposed term “mollusc” is consistent with the current legislation for labelling of food and medicines in Australia. Food Standards Australia New Zealand (FSANZ) requires food to be labelled with “Contains mollusc” where applicable (Food Standards Australia New Zealand, 2020), with a transition period ending in Feb 2024 (Food Standards Australia New Zealand, 2021). FSANZ has discussed their reasoning for identifying ‘mollusc’ and ‘crustacea’ as individual allergens rather than requiring food to be labelled with the umbrella term ‘shellfish’ (Food Standards Australia New Zealand, 2020, pp. 38-39); some consumers are allergic to crustacea and not molluscs, and vice versa, and therefore more specific label statements were required to inform consumers’ choice. The term ‘shellfish’ is also not currently used in non-prescription medicine labelling, as TGO 92 requires ‘Contains crustacea’ on the product label of applicable medicines. Use of the more specific term ‘mollusc’ rather than ‘shellfish’ avoids consumer confusion in the broader context of allergen labelling in food and medicines, and will increase the safety of consumers by promoting consistency in labelling across foods and medicines.

A respondent expressed concerns that the proposed changes would result in fractionation of allergen labelling requirements for complementary medicines across legislation. The ingredients identified in this consultation as mollusc or mollusc derived are currently only used in the listed medicines framework, and it is appropriate to address via the instrument that specifies requirements for ingredients in that framework. However, should TGO 92 be updated in the future to require a label warning to address the allergenicity of molluscs, then the TGA would review the requirements in the Determination to reduce the duplication of requirements across legislative instruments.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. The following 8 ingredients, being mollusc-derived ingredients, will be amended within the Permissible Ingredients Determination commencing on 1 March 2022 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

Affected ingredients

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

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
CONCENTRATED SQUID OMEGA-3 TRIGLYCERIDES	<p>Only for oral use.</p> <p>'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.</p> <p>The medicine requires the following warning statement on the medicine label: - (SFOOD) 'Derived from seafood'.</p>	<p>Only for oral use.</p> <p>'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.</p> <p>The medicine requires the following warning statement on the medicine label: -(SFOOD) 'Derived from seafood'.</p> <p>The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'</p>
GREEN LIPPED MUSSEL		<p>The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'</p>
GREEN LIPPED MUSSEL DRIED		<p>The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'</p>

Ingredient name	Existing specific requirements	New specific requirements
GREEN LIPPED MUSSEL OIL		The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'
OYSTER		The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'
OYSTER SHELL		The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'
SEPIA	Only for use as an active homoeopathic ingredient.	Only for use as an active homoeopathic ingredient. The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'
SQUID OIL	Only for use in oral medicines. The medicine requires the following warning statement on the medicine label: - (SFOOD) 'Derived from seafood'. 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. The medicine requires the following warning statement on the medicine label: -(SFOOD) 'Derived from seafood'. 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. The following warning statement is required on the medicine label: - (MOLLUSC) 'Contains mollusc' or 'Contains mollusc products.'

2. Peripheral neuropathy associated with lower dose vitamin B6

Background

The TGA proposed specific requirements to address the risk of peripheral neuropathy associated with vitamin B6 intake at doses lower than 50 mg/day. Further details regarding the background of this issue and the proposed changes are included in the [Consultation Document](#) provided on the Consultation Hub.

Consultation submissions

Four respondents fully supported the changes as proposed. There was also general agreement with introducing the proposed dose limits for children. However, there were widely varying responses to the remainder of the proposal. Some respondents suggested keeping existing requirements, introducing more restrictive requirements than proposed, while others suggested the existing requirements be relaxed. The following issues were raised in the responses:

- **Maximum daily dose:** the responses recommended a range of maximum daily dose limits from 10 mg to 200 mg equivalent pyridoxine per day. Some responses proposed a 100 mg per day limit, reasoning that there is evidence of clinical benefit at 75-100 mg per day for conditions like premenstrual syndrome and nausea, which would align with certain international agencies and can be revisited as new information emerges. Others supported maintaining the existing 200mg per day limit stating that this dose was of low risk, and that the literature and adverse event information only suggested that higher doses and long durations of exposure were associated with peripheral neuropathy.
- **Duration of use:** some responses suggested that it may not be appropriate to apply limits to all listed medicines, which may be used for other indications, when those limits were based on long-term supplemental use. Other responses recommended that peripheral neuropathy only occurs after long term use (months to years) or at high doses, and the warning statement and restrictions should only be required for products that are taken in these situations. Some responses suggested a 3 or 6 month limit on the duration of use at different doses.
- **Warning statement:** Several responses recommended amending the warning statement to include the total recommended daily dose of vitamin B6 of the medicine on the label (as a total of all forms of vitamin B6). A number of responses raised concerns with describing the symptoms of peripheral neuropathy, reasoning that this would deter consumers from taking supplements, and may cause confusion for patients who had been prescribed vitamin B6 to treat vitamin B6 deficiency, which can include symptoms of peripheral neuropathy.

Some responses supported the proposal that the warning statement should apply for doses of vitamin B6 more than 10mg while others suggested it should remain as 50mg or be changed to 100mg per day, or in line with the National Health and Medical Research Council (NHMRC) upper limits according to age ranges. Some responses suggested there

should be an additional warning for doses more than 50mg per day to avoid prolonged use, while others suggested the label of the medicine could be required to advise consumers not to exceed the existing maximum daily dose (200mg per day).

- **Form of vitamin B6:** one respondent provided some evidence that peripheral neuropathy is more associated with the pyridoxine form (in contrast to the pyridoxal forms). They recommended that the proposed changes only be applied to pyridoxine and not pyridoxal and that the existing requirements for pyridoxal forms be removed. Others proposed the requirements should pertain to all forms of B6.

TGA response

Maximum daily dose and duration of use

There was general support for the proposed dose limits for children. However, one respondent stated they did not agree with the proposed dose limits for children over 12 as this was not supported by the evidence, without providing any further details. The upper limits for younger age groups were specified based on metabolic body size and growth considerations (National Health and Medical Research Council, 2005) and the TGA considers that younger populations should be provided appropriate protections that account for these differences.

There were a range of responses regarding the proposed maximum recommended daily dose for adults, with some respondents recommending that the dose be kept at 200 mg of pyridoxine per day or lowered to 100 mg per day in line with several international agencies. Several submissions noted that vitamin B6 is used on a short-term basis to treat conditions including nausea during pregnancy and premenstrual syndrome at doses up to 100 mg per day (Natural Medicines Database, 2021).

Some responses asserted that this issue is of sufficiently low risk to not warrant changes to regulation, reasoning that the general consensus in the literature is that vitamin B6 is only associated with peripheral neuropathy when taken in high doses or for long periods of time, and that cases of neuropathy from doses less than 50 mg per day were reported rarely. The TGA has previously considered the older literature that described peripheral neuropathy associated with higher doses and longer duration exposure, and has currently proposed regulatory changes as more recent literature and adverse event data describes peripheral neuropathy associated with vitamin B6 at daily doses below 50 mg and at durations of use less than 3 months.

A respondent provided data comparing the number of spontaneous reports of adverse events with sales data of vitamin B6 products in Australia and suggested that the frequency of reported cases is very low. Spontaneous adverse event reporting cannot be relied on to estimate the frequency of adverse events, due to both underreporting and because neither spontaneous reporting nor sales data provide accurate information on the number of people exposed to the medicine. Under-reporting is also expected to be significant considering the absence of a label warning on products with daily doses of 50 mg and below, a lack of consumer awareness of the association with neurotoxicity at lower doses, and the reduced likelihood symptoms would be attributed to listed medicines due to the general perception that vitamins and supplements are safe. There are many listed medicines that contain vitamin B6 that are not marketed or named as a vitamin B6 medicine, further contributing to the lack of awareness for the potential for

peripheral neuropathy. Of the 27 cases of neuropathy and/or elevated blood levels of vitamin B6 reported to the TGA, 7 (26%) described confusion or a lack of awareness of whether the listed medicine they consumed was a source of vitamin B6. Similarly, some respondents, including the Australia and New Zealand Association of Neurologists (ANZAN), noted that peripheral neuropathy had been observed in patients taking supplements (particularly polypharmacy and lower doses) and that patients and their doctors had not been aware those products contained vitamin B6.

Up to 26 November 2021, the TGA has received 27 cases with sufficient information to establish a possible causal association between peripheral neuropathy and medicines containing vitamin B6. Other cases with confounding factors, such as concomitant medicines associated with peripheral neuropathy, were excluded from this figure. Of the cases reported to the TGA:

- 18 (66%) reported elevated vitamin B6 blood levels along with peripheral neuropathy symptoms
- 16 (59%) cases involved a daily dose of 50 mg or less equivalent pyridoxine
- 12 (44%) cases involved daily doses between 22-50 mg equivalent pyridoxine
- 4 (15%) cases involved daily doses less than 21 mg equivalent pyridoxine (3 of which reported elevated vitamin B6 blood levels along with peripheral neuropathy symptoms)

Of the 11 cases where more than 50 mg equivalent pyridoxine per daily dose was reported:

- 7 cases reported taking multiple medicines containing vitamin B6 (polypharmacy)
- 4 cases involved one or more low dose medicines not required to display the label warning.

A recent analysis of data from the Netherlands Pharmacovigilance Centre Lareb (Vrolijk, et al., 2020), which was also referred to by respondents to this consultation, also reports cases of vitamin B6-related neuropathy associated with doses of less than 21 mg per day, and further review (Hadstein & Vrolijk, 2021) notes 'the minimum dose and treatment duration necessary to elicit neuropathy has not been firmly established.' The paper also notes that there are a number of recent case reports of peripheral neuropathy in people taking pyridoxine at doses near or below 25 mg per day, and there is a 'possibility of significant interindividual differences in sensitivity to [pyridoxine] toxicity' (Hadstein & Vrolijk, 2021). While there may be a subpopulation that are more sensitive to this neurotoxicity, this subpopulation has not been identified. Of the 27 cases reported to the TGA, 9 (33%) reported 3 months or less between commencement of supplemental vitamin B6 and onset of neuropathy symptoms. Of these 9 reports, 6 involved daily doses of 50 mg or less pyridoxine equivalent.

There is an international recognition of a risk of neurotoxicity from low-dose pyridoxine supplements, which should be conveyed to consumers.

Warning statement

Some respondents raised concerns that warning statements may discourage consumers from taking supplements. Another respondent suggested that access to vitamin B6 should not be restricted unless there is a serious safety risk and consumers determine risk-benefit consideration when choosing to take a listed medicine. The TGA considers that the existing label warning statement noted in the consultation alerts consumers to the risks associated with

products and provides the opportunity to make an informed choice between the risks and benefits of taking a product. Other suggested approaches in response to the consultation, such as only referring to “contains B6” or stating the maximum daily dose that consumers should not exceed, do not provide sufficient information to make an informed choice or advise the consumer of what action to take if symptoms occur.

Some respondents suggested that medicines indicated for shorter durations, such as 3 months, should be exempt from the warning statement. However, as stated above, no minimum treatment duration to elicit neuropathy symptoms has been established. Prior to 2011, the Required Advisory Statements for Medicine Labels (RASML) required a vitamin B6 warning statement which referred to risks associated with use for “a long period.” As it was not clear what duration “a long period” was (Complementary Medicines Evaluation Committee, 2008), the warning statement was amended to instead inform consumers to the early warning signs of vitamin B6 toxicity and the action to be taken if these should arise.

It is important for consumers to know to stop consuming vitamin B6 if symptoms appear, as peripheral neuropathy may be reversible if ceased soon after symptom onset (Institute of Medicine, 1998); however, symptoms of neuropathy have been observed to increase for short periods following cessation of B6 exposure, and this phenomenon is not associated with elevated blood levels of vitamin B6 (Berger, et al., 1992). Some authors report that recovery can be up to 3 years (Hadstein & Vrolijk, 2021) whilst others report that neurologic dysfunction usually resolves within six months, but that some patients do not recover (Hemminger & Wills, 2021). The preferred treatment of vitamin B6 neuropathy is to cease exposure to vitamin B6 (Hammond, et al., 2013).

Other responses proposed that the risk of peripheral neuropathy from lower dose medicines may be addressed by requiring such products to instead refer to the total amount of vitamin B6 provided by the medicine, as this would provide a greater consumer awareness when taking multiple products containing vitamin B6 (polypharmacy). However, this approach alone does not inform consumers of the risks associated with lower-dose products taken by themselves (or in combination) and as discussed above, does not inform consumers of how to address symptoms if they occur. The existing warning statement also requires the words ‘Contains vitamin B6’ which would help identify polypharmacy concerns if applied to medicines with doses of vitamin B6 under 50mg per day and reduce the risk of consumption of multiple products with vitamin B6 resulting in additive effects.

As both deficiency and excess of vitamin B6 may result in symptoms of neuropathy (Hadstein & Vrolijk, 2021), listed medicines, which may be available without health professional advice, must carry an appropriate warning statement to advise consumers to cease taking and seek medical attention rather than taking more vitamin B6 if symptoms of neuropathy are experienced. Some responses suggested that the proposed warning statement may confuse consumers that are prescribed vitamin B6 by doctors, as a treatment for peripheral neuropathy. Listed medicines are not permitted to make indications related to treatment of serious forms of disease, such as peripheral neuropathy. If a treating doctor elects to prescribe a medicine, the doctor will be able to inform the patient of proper use of the medicine, the risks associated with the medicine, and how they relate to the patient’s specific condition.

As no minimum duration of exposure or daily dose has been established, and there are cases reporting neuropathy symptoms within 3 months or less, medicines indicated for shorter durations should alert consumers of what symptoms to be aware of and to discontinue use for a product to remain of sufficient low-risk to be suitable for medicines available without the intervention of a health care professional.

Form of vitamin B6

A response suggested that the proposed (and existing) requirements for vitamin B6 should be limited to the pyridoxine forms only, citing data suggesting that the pyridoxal form is responsible for toxic effects on neuronal cells, and that peripheral neuropathy is reported more frequently with medicines containing the pyridoxine form. The TGA has received 5 (19%) adverse event reports of peripheral neuropathy from patients taking both pyridoxine and pyridoxal forms, but no reports where pyridoxal was the sole suspected form of vitamin B6. However, there are cases reported internationally of peripheral neuropathy associated with the pyridoxal form only (Vrolijk, et al., 2020). Although a relatively small number of cases were associated with pyridoxal, this data nevertheless indicates that pyridoxal can cause peripheral neuropathy. The reduced frequency of reported adverse events for pyridoxal may be attributed to the fact that the majority of supplements available on the market both in Australia and overseas contain the pyridoxine form.

Summary

The responses highlight considerable uncertainty surrounding this issue. There is no minimum dose, minimum duration of use, form of vitamin B6 and/or identified patient risk factors that are established for peripheral neuropathy to develop. The TGA notes that the risk appears to vary depending on individual differences, and the risk of long term injury is reduced when ceased quickly. The TGA is aware that adverse events have been reported for products with a daily dose below 21 mg (domestically and internationally), in different forms of vitamin B6, or with shorter durations of use (less than 3 months).

The consultation responses also highlight that vitamin B6 products may be indicated for shorter durations than those assessed by the NHMRC. The proposed maximum daily dose for individuals aged 19 and above will be amended to permit up to 100 mg and not 50mg as proposed in the consultation document, and the maximum dose for other age groups will remain as proposed. As a minimum duration of use required to induce peripheral neuropathy was not able to be established, an alternative warning statement for medicines with a shorter recommended duration of use is not appropriate. The current warning statement, applied to products that provide more than 10 mg of vitamin B6, sufficiently mitigates this risk by alerting consumers of the symptoms and what action to take, as well as addressing polypharmacy from lower dose medicines by stating “contains vitamin B6” for all forms. Applying this warning statement to products that only contain more than 30 mg, as suggested by one respondent, does not account for the reports of peripheral neuropathy associated with products below 21 mg of vitamin B6.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. The 3 vitamin B6 ingredients will be amended within the Permissible Ingredients Determination commencing on 1 March

2022 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

The TGA will continue to monitor the developing evidence and adverse events related to this issue and whether the new requirements will be sufficient to mitigate the risk of peripheral neuropathy associated with vitamin B6 intake from listed medicines.

Affected ingredients

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

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
PYRIDOXAL 5-PHOSPHATE	<p>Pyridoxine is a mandatory component of Pyridoxal 5-phosphate.</p> <p>The percentage of pyridoxine from pyridoxal 5-phosphate should be calculated based on the molecular weight of pyridoxal 5-phosphate.</p> <p>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.</p> <p>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: - (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].'</p>	<p>Pyridoxine is a mandatory component of Pyridoxal 5-phosphate.</p> <p>The percentage of pyridoxine from pyridoxal 5-phosphate should be calculated based on the molecular weight of pyridoxal 5-phosphate.</p> <p>The maximum recommended daily dose of the medicine must not provide more than: (a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive); (b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive); (c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive); (d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and (e) 100 mg of pyridoxine for individuals aged 19 years and older.</p> <p>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: - (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].'</p>

Ingredient name	Existing specific requirements	New specific requirements
<p>PYRIDOXAL 5-PHOSPHATE MONOHYDRATE</p>	<p>Pyridoxine is a mandatory component of Pyridoxal 5-phosphate monohydrate.</p> <p>The percentage of pyridoxine from pyridoxal 5-phosphate monohydrate should be calculated based on the molecular weight of pyridoxal 5-phosphate monohydrate.</p> <p>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.</p> <p>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: - (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].'</p>	<p>Pyridoxine is a mandatory component of Pyridoxal 5-phosphate monohydrate.</p> <p>The percentage of pyridoxine from pyridoxal 5-phosphate monohydrate should be calculated based on the molecular weight of pyridoxal 5-phosphate monohydrate.</p> <p>The maximum recommended daily dose of the medicine must not provide more than: (a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive); (b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive); (c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive); (d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and (e) 200 100 mg of pyridoxine for individuals aged 19 years and older.</p> <p>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: - (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].'</p>

Ingredient name	Existing specific requirements	New specific requirements
<p>PYRIDOXINE HYDROCHLORIDE</p>	<p>When not used as an active homoeopathic ingredient, pyridoxine is a mandatory component of Pyridoxine hydrochloride.</p> <p>The percentage of pyridoxine from pyridoxine hydrochloride should be calculated based on the molecular weight of pyridoxine hydrochloride.</p> <p>The maximum recommended daily dose must provide no more than 200 mg of pyridoxine.</p> <p>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: - (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].'</p>	<p>When not used as an active homoeopathic ingredient, pyridoxine is a mandatory component of Pyridoxine hydrochloride.</p> <p>The percentage of pyridoxine from pyridoxine hydrochloride should be calculated based on the molecular weight of pyridoxine hydrochloride.</p> <p>The maximum recommended daily dose of the medicine must not provide more than: (a) 15 mg of pyridoxine for children aged between 1 and 3 years (inclusive); (b) 20 mg of pyridoxine for children aged between 4 and 8 years (inclusive); (c) 30 mg of pyridoxine for children aged between 9 and 13 years (inclusive); (d) 40 mg of pyridoxine for individuals aged 14 and 18 years (inclusive); and (e) 200 100 mg of pyridoxine for individuals aged 19 years and older.</p> <p>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: - (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].'</p>

3. Risk to infants from nasal use of benzalkonium chloride

Background

The TGA proposed specific requirements 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. Further details regarding the background of this issue and the proposed changes are included in the [Consultation Document](#) provided on the Consultation Hub.

Consultation submissions

All respondents agreed with the need to restrict benzalkonium chloride use in nasal sprays for infants. One respondent recommended that the warning statement be amended to 'Not to be used by children under 2 years old' rather than 'Not to be taken by children under 2 years old'. Another respondent recommended that restrictions should also be implemented for use of nasal sprays containing benzalkonium in all ages, due to the risk of bronchospasm and asthma, and recommended a limit of 0.2% concentration benzalkonium chloride in all nasal sprays. Another respondent requested clarification of whether the proposed restrictions for nasal sprays would be extended to other medicines for nasal application such as drops.

TGA response

The TGA agrees that reference of the warning statement to 'used by' is more appropriate than 'taken by' in the context of a nasal spray medicine administered to infants.

The effect of benzalkonium chloride on other age groups is also of concern, and evidence provided indicates that exposure to benzalkonium chloride can cause sensitisation and allergic response, including bronchospasm among asthmatics (Lechien, et al., 2018) (George, et al., 2017) (Kim & Ahn, 2004) (Mizkiel, et al., 1988). The TGA has not previously considered an appropriate maximum limit for the concentration of benzalkonium chloride in nasal sprays in listed medicines. The highest concentration of benzalkonium chloride in registered medicine nasal sprays is not more than 0.03% (as of 22 November 2021). There are currently no listed medicine nasal sprays that contain benzalkonium chloride above this concentration. In the absence of a safety assessment of benzalkonium chloride as a listed medicine ingredient demonstrating safety at the current 5% restriction, the use in listed medicines should be limited, as a baseline, to 0.03% in line with other pre-market evaluated nasal sprays.

The TGA notes that benzalkonium chloride is only permitted for use when applied dermally or as a nasal spray and, as such, the requirements have no impact on other dosage forms including nasal drops.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. Benzalkonium chloride will be amended within the Permissible Ingredients Determination commencing on 1 March 2022 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
<p>BENZALKONIUM CHLORIDE</p>	<p>Only for use in topical medicines for dermal application and nasal sprays.</p> <p>The concentration in the medicine must be no more than 5%.</p>	<p>Only for use in topical medicines for dermal application and nasal sprays.</p> <p>When benzalkonium chloride is used in a topical medicine for dermal application, the concentration in the medicine must not be more than 5%.</p> <p>When benzalkonium chloride is used in a nasal spray dosage form, the concentration of benzalkonium chloride in the medicine must not be more than 0.03%.</p> <p>When benzalkonium chloride is used in a nasal spray dosage form which is either:</p> <ul style="list-style-type: none"> a) indicated for use in children; or b) not specifically indicated for adults only; <p>the following warning statement is required on the medicine label:</p> <ul style="list-style-type: none"> - 'Not to be used by children under 2 years old' (or words to that effect).

4. Artemisinin and pregnancy risk

Background

The TGA proposed specific requirements to address the pregnancy risk associated with the intake of artemisinin from certain *Artemisia* species. Further details regarding the background of this issue and the proposed changes are included in the [Consultation Document](#) provided on the Consultation Hub.

Consultation submissions

Four respondents supported the proposed changes. A number of respondents recommended that a warning statement should not be required for essential oils of *Artemisia* species when used in flavours or fragrances, as artemisinin has not been detected in the essential oils and their use in flavours and fragrances are considerably dilute. It was also suggested that the warning statement not be required for products intended for topical medicines for dermal application.

One respondent commented that the safety profile of a herbal ingredient should consider whole plant ingredients, rather than a single component, and noted that the TGA should give consideration to differences in risks between self-selected medicines and medicine provided by a health professional

TGA response

Vulnerable populations such as pregnant women, need to be informed of the risks associated with listed medicines, including the risk of toxicity from artemisinin during pregnancy. The TGA considers that pregnant populations, and those intending to become pregnant, should not be exposed to this risk. The Naturopaths & Herbalists Association of Australia (NHAA) supported a warning statement for self-selected medicines and noted their assessment that the use of artemisinin containing herbs during pregnancy should be under the supervision of a health professional.

Davana oil was included in this consultation due to the identification of artemisinin in *A. pallens*, from which davana oil is extracted as an essential oil. A number of respondents stated that artemisinin has not been detected in the essential oils of the identified species. A recent study published after the responses were received (Singh, et al., 2021) identified 97.1% of the chemicals within davana oil, and did not report artemisinin as a component, and a study on the composition of steam distilled *Artemisia dracunculus* essential oil identified 99.6% of components, and did not identify artemisinin (Fildan, et al., 2019).

Artemisinin is known to be heat-sensitive, and has been observed to degrade during essential oil extraction by steam distillation of *Artemisia* species (Jeng Lin, et al., 1985) (Ferreira, et al., 2013). As such, the steam distillation process reduces the risk of artemisinin being present in *Artemisia* essential oils, including davana oil. Further, the use of an essential oil as a part of a proprietary flavour or fragrance ingredient reduces the risk of artemisinin being present in the final medicine composition, as flavours and fragrances are only permitted up to 5% and 1% concentrations (respectively) in the finished product. Based on the currently available

information, it appears that the risk of artemisinin being present in a medicine from a steam-distilled essential oil of an *Artemisia* species, as part of a flavour or fragrance, is sufficiently low that the application of the warning statement regarding use during pregnancy is not required.

A number of respondents suggested that the issue may only be relevant to oral intake; however, no data was provided to support the safety of artemisinin, such as dermal absorption of artemisinin, when applied topically for dermal use. The TGA is not aware of any data to establish that the risk of embryotoxicity from artemisinin is different when applied topically for dermal use.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. Davana oil is no longer proposed to be amended. Three *Artemisia* species, which are available for use as excipients, will not be required to carry the warning statement when prepared as a steam-distilled essential oil used in flavour or fragrance formulation. The following 4 ingredients will be amended within the Permissible Ingredients Determination commencing on 1 March 2022 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

Affected ingredients

- ARTEMISIA DRACUNCULUS
- ARTEMISIA FRIGIDA
- ARTEMISIA PALLENS
- ARTEMISIA VULGARIS

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
ARTEMISIA DRACUNCULUS	<p>Thujone is a mandatory component of Artemisia dracunculus.</p> <p>The concentration of thujone from Artemisia dracunculus in the medicine must be no more than 4%.</p>	<p>Thujone is a mandatory components of Artemisia dracunculus.</p> <p>The concentration of thujone from Artemisia dracunculus in the medicine must be no more than 4%.</p> <p>The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect); unless the ingredient is: (a) a steam-distilled essential oil, and (b) for use in combination with other permitted ingredients as part of a fragrance or flavour proprietary excipient formulation where: (i) the total concentration of fragrance proprietary excipient formulations containing Artemisia dracunculus is not more than 1% of the total medicine; or (ii) the total concentration of flavour proprietary excipient formulations containing Artemisia dracunculus is not more than 5% of the total medicine.</p>
ARTEMISIA FRIGIDA	<p>Thujone is a mandatory component of Artemisia frigida.</p> <p>The concentration of thujone from Artemisia frigida in the medicine must be no more than 4%.</p>	<p>Thujone is a mandatory component of Artemisia frigida.</p> <p>The concentration of thujone from Artemisia frigida in the medicine must be no more than 4%.</p> <p>The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect.</p>

Ingredient name	Existing specific requirements	New specific requirements
ARTEMISIA PALLENS	<p>Thujone is a mandatory component of Artemisia pallens.</p> <p>The concentration of thujone from Artemisia pallens in the medicine must be no more than 4%.</p>	<p>Thujone is a mandatory component of Artemisia pallens.</p> <p>The concentration of thujone from Artemisia pallens in the medicine must be no more than 4%.</p> <p>The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect); unless the ingredient is: (a) a steam-distilled essential oil, and (b) for use in combination with other permitted ingredients as part of a fragrance or flavour proprietary excipient formulation where: (i) the total concentration of fragrance proprietary excipient formulations containing Artemisia pallens is not more than 1% of the total medicine; or (ii) the total concentration of flavour proprietary excipient formulations containing Artemisia pallens is not more than 5% of the total medicine.</p>
ARTEMISIA VULGARIS	<p>Thujone is a mandatory component of Artemisia vulgaris.</p> <p>The concentration of thujone from Artemisia vulgaris in the medicine must be no more than 4%.</p>	<p>Thujone is a mandatory component of Artemisia vulgaris.</p> <p>The concentration of thujone from Artemisia vulgaris in the medicine must be no more than 4%.</p> <p>The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant' (or words to that effect); unless the ingredient is: (a) a steam-distilled essential oil, and (b) for use in combination with other permitted ingredients as part of a fragrance or flavour proprietary excipient formulation where: (i) the total concentration of fragrance proprietary excipient formulations containing Artemisia vulgaris is not more than 1% of the total medicine; or (ii) the total concentration of flavour proprietary excipient formulations containing Artemisia vulgaris is not more than 5% of the total medicine.</p>

Timetable

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

The transition period of 12 months 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

- Berger, A. R. et al., 1992. Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy: a prospective study of pyridoxine neurotoxicity. *Neurology*, 42(7), pp. 1367-70.
- Complementary Medicines Evaluation Committee, 2008. *Extracted Ratified Minutes - 65th Meeting*, Canberra: Therapeutic Goods Administration.
- Ferreira, F. S., Zheljaskov, V. D. & Gonzalez, J. M., 2013. Artemisinin concentration and antioxidant capacity of *Artemisia annua* distillation byproduct. *Industrial Crops and Products*, Volume 41, pp. 294-298.
- Fildan, A. P. et al., 2019. *Artemisia dracunculus* Essential Oil: Chemical composition and antioxidant properties. *Revista de Chimie*, 70(12), pp. 59-62.
- Food Standards Australia New Zealand, 2020. *Approval report - Proposal P1044: Plain English Allergen Labelling*. [Online]
Available at:
<https://www.foodstandards.gov.au/code/proposals/Documents/P1044%20Approval%20Report.pdf>
[Accessed 15 November 2021].
- Food Standards Australia New Zealand, 2021. *New requirements for allergen labelling on packaged foods*. [Online]
Available at: <https://www.foodstandards.gov.au/media/Pages/New-requirements-for-allergen-labelling-on-packaged-foods.aspx>
[Accessed 15 November 2021].
- George, M., Joshi, S. V., Concepcion, E. & Lee, H., 2017. Paradoxical bronchospasm from benzalkonium chloride (BAC) preservative in albuterol nebulizer solution in a patient with acute severe asthma. A case report and literature review of airway effects of BAC. *Respiratory Medicine Case Reports*, Volume 21, pp. 39-41.
- Hadstein, F. & Vrolijk, M., 2021. Vitamin B-6 Induced Neuropathy: Exploring the mechanisms of pyridoxine toxicity. *Advances in Nutrition*, 12(5), pp. 1911-1929.
- Hammond, N., Wang, Y., Dimachkie, M. M. & Barohn, R. J., 2013. Nutritional neuropathies. *Neurologic clinics*, 31(2), pp. 477-489.
- Hemminger, A. & Wills, B. K., 2021. *Vitamin B6 Toxicity*, Treasure Island, FL, USA: StatPearls Publishing.
- Institute of Medicine, 1998. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Chapter 7: Vitamin B6*, Washington, DC: National Academy Press.
- Jeng Lin, A. et al., 1985. Thermal rearrangement and decomposition products of artemisinin (qinghaosu). *The Journal of Organic Chemistry*, 50(23), pp. 4504-4508.
- Kim, S.-H. & Ahn, Y., 2004. Anaphylaxis Caused by Benzalkonium in a Nebulizer Solution. *Journal of Korean Medical Science*, 19(2), pp. 289-90.
- Lechien, J. R. et al., 2018. Contact allergy to benzalkonium chloride in patients using a steroidal nasal spray: A report of 3 cases. *Ear, nose, & throat journal*, 97(1-2), pp. E20-E22.

Mizkiel, K. A., Beasley, R. & Holgate, S. T., 1988. The influence of ipratropium bromide and sodium cromoglycate on benzalkonium chloride-induced bronchoconstriction in asthma. *British journal of clinical pharmacology*, 26(3), pp. 295-301.

National Health and Medical Research Council, 2005. *Nutrient Reference Values for Australia and New Zealand - Vitamin B6*, s.l.: s.n.

Natural Medicines Database, 2021. *Monograph for Vitamin B6*. [Online] Available at: <https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=934> [Accessed 8 December 2021].

Singh, et al., 2021. New Insights into the Chemical Composition, Pro-Inflammatory Cytokine Inhibition Profile of Davana (*Artemisia pallens* Wall. ex DC.) Essential Oil and cis-Davanone in Primary Macrophage Cells. *Chemistry & Biodiversity*, 18(11), p. e2100531.

Vrolijk, M. F. et al., 2020. Interindividual differences in pharmacokinetics of vitamin B6: A possible explanation of different sensitivity to its neuropathic effects. *PharmaNutrition*, Volume 12.

Version history

Version	Description of change	Author	Effective date
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