Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Notice of interim decision to amend (or not amend) the current Poisons Standard in relation to pyridoxine, pyridoxal or pyridoxamine (vitamin B6)

26 June 2025

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

Notice of interim decisions made under Regulation 42ZCZN of the Therapeutic Goods Regulations 1990

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decision made by a delegate of the Secretary of the Department of Health, Disability and Ageing responsible for scheduling of medicines and chemicals (the **Delegate**)[1] under regulation 42ZCZN in relation to proposed amendment to the current Poisons Standard which was referred to an expert advisory committee[2] under subdivision 3D.2 of the Regulations in November 2024;
- the proposed date of effect of the proposed amendment.

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to this interim decision on or before 27 July 2025.

Submissions should be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

Defined terms

In this notice the following defined terms are used in addition to those above:

- the *Therapeutic Goods Act 1989* (Cth) (the Act)
- the Scheduling Policy Framework 2018 (the SPF)
- the Scheduling handbook: Guidance for amending the Poisons Standard (the Handbook), and
- the Therapeutic Goods Administration (the TGA).

Note: additional terms are also defined for individual decisions.

[1] For the purposes of s 52D of the *Therapeutic Goods Act 1989* (Cth)

[2] Established under sections 52B and 52C of the *Therapeutic Goods Act 1989* (Cth).

Interim decision on a proposed amendment referred to the Advisory Committee on Medicines Scheduling (ACMS #46, November 2024)

Interim decision in relation to pyridoxine, pyridoxal or pyridoxamine

Proposal

The applicant has proposed to amend the current Poisons Standard in relation to pyridoxine, pyridoxal or pyridoxamine which are different forms of vitamin B6. Under the proposal, human therapeutic preparations containing between 5 mg and 200 mg of pyridoxine, pyridoxal or pyridoxamine would be included in a new Pharmacist Only Medicine (Schedule 3) entry. These preparations are currently not scheduled.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to pyridoxine, pyridoxal or pyridoxamine as follows:[3]

Schedule 4 – Amend entry

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE for human therapeutic use **except:**

(a) when included in Schedule 3; or ~~in oral preparations containing 200 mg or less but more than 50 mg of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose when compliant with the requirements of the required advisory statements for medicine labels; or~~

(b) in oral preparations containing 50 mg or less of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

Schedule 3 – New Entry

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE for human therapeutic use in oral preparations containing more than 50 mg but less than 200 mg of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

Index – New /Amend/ Delete Entry

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE

Schedule 4

Schedule 3

[3] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to pyridoxine, pyridoxal or pyridoxamine (the Application)
- The 21 public submissions, with 20 including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the Submissions)
- The advice received from the 46th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current scheduling of pyridoxine, pyridoxal or pyridoxamine remains appropriate. The Committee considered that consumer behaviour and lack of awareness are the major drivers for the adverse events generally associated with vitamin B6 over-consumption. The Committee advised that scheduling is not the appropriate regulatory instrument to control the risk of overconsumption from multiple sources and there is not enough information to justify the amendments proposed by the applicant. Instead, the Committee recommended that that the TGA should consider:

- education campaigns to increase public awareness of adverse effects of overconsumption of vitamin B6
- using ‘vitamin B6’ instead of ‘pyridoxine’ on labels for better consumer understanding
- strengthening the labelling requirements either through stronger wording of warning statements and/or clearer labelling for the presence of vitamin B6 in products.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice include:

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

Risks:

– Vitamin B6 can be consumed at doses higher than the recommended daily intake, including through the consumption of a variety of supplement products.

– Predominantly high doses and/or prolonged use has been linked with peripheral neuropathy. However, there are case reports at low doses and consensus regarding a safe threshold is lacking.

Benefits:

– Limited data is available for the benefit of vitamin B6 for pre-menstrual symptoms and pregnancy-related nausea and vomiting.

- There is very limited data regarding the benefit of vitamin B6 for cardiovascular disease prevention and general wellbeing.
- Higher doses have a minor use in treating rare paediatric epilepsy syndromes.

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

- Used to treat vitamin B6 deficiency.
- Included in large number of supplements with a variety of listed benefits including use in treating pre-menstrual symptoms, pregnancy-related nausea and vomiting, prevention of cardiovascular diseases and stress management.

c) the toxicity of a substance

- Vitamin B6 has been associated with peripheral neuropathy generally at high doses (>500 mg/day) and prolonged duration but cases at lower doses have been reported.
- There is uncertainty regarding a safe daily dose and a large variation in daily upper limits set by different countries.

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

- Presented as capsules, tablets, liquids, chewable tablets and sublingual tablets.
- Can be single ingredient or included in multi-ingredient preparations.
- Dosage ranges from less than 2 mg to 100 mg recommended daily dose (RDD) which are currently unscheduled (when compliant with the requirements of the Required Advisory Statements for Medicine Labels); higher doses (> 200 mg) are available on prescription.
- Presence of vitamin B6 in multi-ingredient products is often not prominently displayed.
- Use of ingredient names in labelling is inconsistent and confusing for consumers (pyridoxine, pyridoxine hydrochloride, pyridoxal 5-phosphate, and pyridoxal 5-phosphate monohydrate are used and not always described as vitamin B6).

e) the potential for abuse of a substance

- Nil.

f) any other matters that the Secretary considers necessary to protect public health

- Lack of consumer awareness of adverse side effects.
- Risk of overconsumption from a variety of sources including dietary, fortified foods, vitamins and supplements (single ingredient and multi-ingredient, including some magnesium formulations providing a daily dose of nearly 100 mg of vitamin B6).
- Increased use of supplements and growing awareness of ability to report may have contributed to increased reports of peripheral neuropathy.

Reasons for the interim decision (including findings on material questions of fact)

While I agree with the Committee's findings on the relevant provisions of section 52E of the Act, I disagree with the Committee's scheduling recommendation to not amend the Poisons Standard. I also disagree with the applicant's proposal to restrict all preparations containing 5-200 mg of vitamin B6 (pyridoxine, pyridoxal or pyridoxamine) as Pharmacist Only medicines (Schedule 3).

I have considered the 17 public submissions received during the pre-meeting consultation of which 15 opposed the proposal and 14 provided written justification for their opposing views. The main points raised in opposition are summarised below.

- Peripheral neuropathy is associated with high dosage (above 100 mg/day) taken over a long period of time and symptoms generally improve after discontinuation.
- Cases of peripheral neuropathy are rare, particularly at dosages below 50 mg/day, and the risk is negligible when compared to the number of products available and large volume of sales.
- Interpretation of data available, including TGA's Database of Adverse Events (DAEN), is limited by the minimal amount of information regarding exact dose consumed, formulation and symptoms recorded (self-observed or diagnosed by medical professional). A causal relationship between higher intake of vitamin B6 and peripheral neuropathy cannot be clearly established.
- The current labelling requirements for listed medicines providing more than 10 mg RDD commenced on 1 March 2022 with a 1-year transition period. Industry considers the new requirements practical and adequate in communicating the risks from excess intake of vitamin B6 and the impact of these regulatory changes are not yet fully realised.
- The proposed cut-off level of 5 mg RDD is not supported in the literature and will impact more than 1,500 listed medicines imposing an immense regulatory burden for sponsors and pharmacies.

One response was fully supportive of the applicant's proposal, and 1 was partially supportive. Both provided written justification for their support. The supporters consider the proposal to be a sensible balance between public health safety and consumer access where pharmacist involvement can address the lack of consumer awareness regarding potential risks associated with consuming multiple products containing vitamin B6.

I disagree with both the Committee's recommendation and the majority view of not amending the scheduling of pyridoxine, pyridoxal or pyridoxamine. In doing so, I have considered the following matters.

Vitamin B6 function

Vitamin B6 is a water-soluble vitamin that acts as a co-enzyme in more than 150 enzymatic reactions in the metabolism of amino acids, carbohydrates and lipids.[4] Vitamin B6 is also important for the synthesis of many neurotransmitters, haemoglobin formation and immune functions. Vitamin B6 deficiency can cause peripheral neuropathy, seborrheic dermatitis, glossitis, and cheilosis, and, in adults, confusion and seizures.

Dietary requirements

Vitamin B6 is found in a wide range of foods including meats, breakfast cereals, vegetables and fruits. In Australia, the estimated average requirement for vitamin B6 for adults is 1.1 to 1.3 mg/day and the recommended dietary intake (RDI) is 1.3 to 1.7 mg/day.[5] Despite many Australians not eating the recommended serves of the 5 food groups each day and consuming a high amount of discretionary food, the nutrient intake of Australians, as a whole, is not adversely affected. Australians generally get enough key nutrients in their diet.[6]

[4] The Enzyme Commission website (www.chem.qmul.ac.uk/iubmb/enzyme/) accessed on 16 June 2025

[5] Nutrient Reference Values for Australia and New Zealand. National Health and Medical Research Council, Australian Government Department of Health, Disability and Ageing, New Zealand Ministry of Health (2006).

[6] Nutrition across the life stages. Australian Institute of Health and Welfare (2018).

For example, based on the vitamin B6 content in various foods, one serve of breakfast cereal (30 g), one cup of mashed potato, one medium banana and one portion of chicken breast (85 g) is expected to provide 2 mg of vitamin B6.[7,8] In Australia, vitamin B6 (pyridoxine hydrochloride) can be added to various food items including bread, breakfast cereals, cereal flours, pasta and formulated beverages. The maximum permissible amount is 0.25 mg (25% RDI) per reference quantity (35 g for bread, pasta and flour). However, formulated caffeinated beverages (colloquially known as energy drinks) can contain up to 10 mg of vitamin B6 in a daily maximum amount of 600 mL, which is almost 6 times the RDI.

Further, human gut flora synthesises vitamin B6 which can make a significant contribution to a person's vitamin B6 intake and may be an additional factor for why dietary vitamin B6 deficiency is rare.[9]

Overall, I am of the view that the RDI for vitamin B6 is easily met through dietary intake alone by most Australians and supplementation is generally only required for people diagnosed with a clinical deficiency of vitamin B6.

Therapeutic use of vitamin B6

Clinical deficiency of vitamin B6 is rare. Vitamin B6 deficiency is usually caused by pyridoxine-inactivating medications (e.g. isoniazid), protein-energy undernutrition, malabsorption, alcohol use disorder, impaired renal function or autoimmune diseases. Diagnosis of vitamin B6 deficiency is based on clinical findings coupled with laboratory measurement of serum pyridoxal 5′-phosphate (PLP) levels. Generally, deficiencies are addressed by correcting the secondary causes or prescribing vitamin B6 supplementation, or both.[10] Vitamin B6 supplementation in therapeutic dose of 10 to 25 mg/day is used to treat seizures from isoniazid toxicity.[11]

Several Australian government guidelines suggest taking doxylamine and pyridoxine tablets (50-200 mg/day) together as a remedy for nausea and vomiting in pregnancy (commonly known as 'morning sickness'), but advocate caution against high intake of vitamin B6.[12,13,14] A recent systematic review of the use of vitamin B6 to treat nausea and vomiting in pregnancy noted that high doses of vitamin B6 may lead to adverse pregnancy outcomes and the potential risks, particularly during the critical first trimester of embryonic development, cannot be ignored.[15]

Supplemental vitamin B6 has been hypothesised to reduce risks of cardiovascular diseases, certain kinds of cancer and loss of cognitive function, but there is little evidence of preventative or beneficial effect of vitamin B6 for these conditions. Conclusive evidence is also lacking on the use of supplemental vitamin B6 (up to 100 mg/day) to treat premenstrual syndrome.[16]

Overall, I consider the benefits of supplemental intake of vitamin B6 to be negligible, unless required to address a clinically diagnosed deficiency.

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[7] Vitamin B6 Fact Sheet for Health Professionals, US National Institute of Health, Office of Dietary Supplements; accessed on 16 June 2025

[8] Nutritional information available from www.kelloggs.com.au; accessed on 16 June 2025.

[9] Wan Z, Zheng J, Zhu Z, Sang L, Zhu J, Luo S, Zhao Y, Wang R, Zhang Y, Hao K, Chen L, Du J, Kan J, He H. Intermediate role of gut microbiota in vitamin B nutrition and its influences on human health. Front Nutr. 2022 Dec 13;9:1031502. doi: 10.3389/fnut.2022.1031502

[10] MSD Manual Professional Version - Vitamin B6 Deficiency and Dependency, accessed on 23 June 2025.

[11] Hemminger A, Wills BK. Vitamin B6 Toxicity. [Updated 2023 Feb 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from www.ncbi.nlm.nih.gov/books/NBK554500/, accessed on 232 June 2025.

[12] Information leaflet on Nausea and Vomiting in Pregnancy, NSW Health, accessed on 23 June 2025

[13] Adult Medication Guideline on Pyridoxine (Vitamin B6), Government of Western Australia, accessed on 23 June 2025.

[14] Guideline for the management of nausea and vomiting in pregnancy and hyperemesis gravidarum. Society for Obstetric Medicine of Australia and New Zealand, accessed on 16 June 2025.

[15] He L, Fan Y, Hu Y, Tian C, Tian Y, Zhang J, Ren Y, Tan J. The potential hazards of high doses of vitamin B6 in treating nausea and vomiting in pregnancy: A systematic review. Int J Gynaecol Obstet. 2025 Apr;169(1):38-50. doi: 10.1002/ijgo.16032.

[16] Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol. 2009 Fall;16(3):e407-29. PMID: 19923637.

Vitamin B6 metabolism

The term vitamin B6 is used to represent a group of 3 related substances (pyridoxine, pyridoxal, and pyridoxamine) and their phosphorylated forms. Of these compounds, PLP – the phosphorylated form of pyridoxal – represents the major biologically active form of vitamin B6, while pyridoxine hydrochloride is the form most commonly used in nutritional supplements and vitamin preparations.

Phosphorylated forms of pyridoxine, pyridoxal, and pyridoxamine are first dephosphorylated in the intestine, absorbed across the intestinal membrane and are re-phosphorylated by pyridoxal kinase. Pyridoxine phosphate and pyridoxamine phosphate are then converted to PLP by the action of pyridoxine phosphate oxidase. This occurs primarily in the liver, after which PLP is circulated in an albumin bound form. The body stores vitamin B6 as PLP covalently bound to glycogen phosphorylase enzyme in muscles.

Because of the reactivity of its aldehyde group, PLP can be involved in other unwanted reactions with macromolecules within the cell, analogous to the unwanted reactions of reactive oxygen species. PLP levels are tightly regulated in the body and intracellular PLP concentrations are maintained at approximately 1 µM to prevent inappropriate reactions (aldehyde or carbonyl stress).[17]

When vitamin B6 intake exceeds requirements, PLP is dephosphorylated (mainly in the liver) to pyridoxal which is then oxidised to pyridoxic acid prior to excretion in urine. Pyridoxal can also be converted to pyridoxine by the action of pyridoxal reductase. Although the body absorbs large pharmacological doses of vitamin B6, it quickly eliminates most but not all of it in the urine.[18]

Pools of vitamin B6 stored in skeletal muscle are resistant to depletion and vitamin B6 supplementation is not associated with marked increases in vitamin B6 in muscle. In contrast, vitamin supplementation can result in an increase in vitamin B6 concentrations in plasma which decreases once supplementation is stopped.[19] The pharmacokinetics of vitamin B6 is also dependent on the vitamer used for supplementation.

Excessive intake of pyridoxine can saturate pyridoxal kinase and pyridoxine phosphate oxidase with a resultant accumulation of inactive pyridoxine which can act then as a competitive inhibitor for PLP dependent enzymes mimicking the symptoms of vitamin B6 deficiency. Differences in metabolism of pyridoxine between individuals may also explain the differences in individual toxicity to vitamin B6.[20,21]

Pyridoxine has also been reported to induce cell death *in vitro* while the other vitamers including pyridoxamine did not. There are several clinical reports on neurological side effects of pyridoxine that discourage the use of excessive pyridoxine.[22, 23, 24]

Adverse effects (peripheral neuropathy)

Peripheral neuropathy is a common neurological disorder that affects the peripheral nervous system in humans, commonly secondary to medical conditions such as diabetes. The prevalence of peripheral

[17] di Salvo ML, Contestabile R, Safo MK. Vitamin B6 salvage enzymes: mechanism, structure and regulation. Biochim Biophys Acta. 2011 Nov;1814(11):1597-608. DOI: 10.1016/j.bbapap.2010.12.006.

[18] Vitamin B6 Fact Sheet for Health Professionals, National Institute of Health, Office of Dietary Supplements, accessed on 16 June 2025.

[19] Van den Eynde MDG, Scheijen JLJM, Stehouwer CDA, Miyata T, Schalkwijk CG. Quantification of the B6 vitamers in human plasma and urine in a study with pyridoxamine as an oral supplement; pyridoxamine as an alternative for pyridoxine. Clin Nutr. 2021 Jul;40(7):4624-4632. DOI: 10.1016/j.clnu.2021.05.028.

[20] Vrolijk MF, Opperhuizen A, Jansen EHJM, Hageman GJ, Bast A, Haenen GRMM. The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. Toxicol In Vitro. 2017 Oct;44:206-212. DOI: 10.1016/j.tiv.2017.07.009.

[21] Vrolijk MF, Hageman GJ, van de Koppel S, van Hunsel F, Bast A. Inter-individual differences in pharmacokinetics of vitamin B6: a possible explanation of different sensitivity to its neuropathic effects. PharmaNutrition. 2020;12:100188. DOI: 10.1016/j.phanu.2020.100188.

[22] de Zegher F, Przyrembel H, Chalmers RA, Wolff ED, Huijmans JG. Successful treatment of infantile type I primary hyperoxaluria complicated by pyridoxine toxicity. Lancet. 1985 Aug 17;2(8451):392-3. DOI: 10.1016/s0140-6736(85)92536-x.

[23] Hammen A, Wagner B, Berkhoff M, Donati F. A paradoxical rise of neonatal seizures after treatment with vitamin B6. Eur J Paediatr Neurol. 1998;2(6):319-22. DOI: 10.1016/s1090-3798(98)80007-x

[24] Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. Eur J Emerg Med. 2005 Apr;12(2):78-85. DOI: 10.1097/00063110-200504000-00007.

neuropathy in the general population ranges from 1% to 7% with higher rates among those older than 50 years and persons with diabetes.[25,26] Despite the vital roles played by vitamin B6 in various bodily functions, it is now well established that high intake of vitamin B6 can lead to the development of peripheral neuropathy. Previously, it was generally considered that high intake greater than 200 mg/day taken over a long period of time is required to develop peripheral neuropathy. However, a recent review by the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens concluded that currently available evidence 'allows establishing with sufficient certainty that peripheral neuropathy may occur at supplemental vitamin B6 intakes of 50 mg/day in some individuals'.[27] In arriving at their conclusion, the panel considered several cases of peripheral neuropathy at supplemental doses of less than 50 mg/day reported in literature and vigilance systems from EU member states. The Panel additionally noted the large inter-individual differences in sensitivity to vitamin B6 toxicity.[28] The case reports, vigilance data and some of the published literature reviewed by the EFSA panel, were not considered in the recent review cited by the public submitters opposing the scheduling proposal.

As of 4 June 2025, there were 174 reports of peripheral neuropathy, peripheral sensory neuropathy, small fibre neuropathy or chronic polyneuropathy for products containing vitamin B6 on the TGA's Database of Adverse Event Notifications (DAEN). Of these, 102 also reported 'Hypervitaminosis B6' and/or 'Vitamin B6 increased'. There were another 92 reports of 'Hypervitaminosis B6' and/or 'Vitamin B6 increased' with less specific reaction terms such as paraesthesia, burning sensation etc. also possibly suggestive of neuropathies.

A majority of the 174 adverse events in DAEN were reported since 1 January 2023 (131 events, 75%) with 36 events being reported in 2023, 41 events in 2024, and 54 events to 4 June 2025. The sustained reporting following the TGA's safety update in 2022 and changes to label warnings for vitamin B6 products (effective 1 March 2022 with a 1 year transition period) indicates that the incidence of adverse events may be higher than the pre-2023 reporting data suggested. The sustained reporting to the TGA, combined with general under-reporting of adverse events for complementary medicines and vitamin supplements perceived as safe, suggests that reports in the DAEN are unlikely to be a result of 'notoriety bias'.

Submissions also referred to the low number of peripheral neuropathies reported in the EudraVigilance database and contrasted that against volume of sales to argue a low frequency of adverse events from vitamin B6 supplementation. I note that the denominator used is unit sale volume rather than number of people taking vitamin B6 supplementation. Further, EudraVigilance is a system for managing and analysing information on suspected adverse reactions to medicines authorised in the European Economic Area (www.ema.europa.eu/en/human-regulatory-overview/pharmacovigilance-overview#monitoring-suspected-adverse-reactions-11758). The EudraVigilance database therefore would include minimal data for products containing vitamin B6 as they are considered food supplements in the EU and are not regulated as medicines (Food supplements | EFSA).

Reporting of adverse events for food supplements is likely dependent on the requirements of individual EU members states. In the Netherlands, adverse events for 'non-registered health-enhancing products' are collected by the Netherlands Pharmacovigilance Centre Lareb. However, the number of reports for these products is far lower than for other medicines.[29] Despite this, between August 2007 until July 2024, Lareb received 238 reports of neuropathic pain associated with the use

[25] Castelli G, Desai KM, Cantone RE. Peripheral Neuropathy: Evaluation and Differential Diagnosis. Am Fam Physician. 2020 Dec 15;102(12):732-739. PMID: 33320513.

[26] Hicks, C.W., Wang, D., Windham, B.G. et al. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Sci Rep 11, 19159 (2021). DOI: 10.1038/s41598-021-98565-w

[27] EFSA Panel on Nutrition, Novel Foods and Food Allergens. Scientific opinion on the tolerable upper intake level for vitamin B6. EFSA Journal 2023;21(5):8006, 110 pp. DOI: 10.2903/j.efsa.2023.8006

[28] Hadtstein F, Vrolijk M. Vitamin B-6-Induced Neuropathy: Exploring the Mechanisms of Pyridoxine Toxicity. Adv Nutr. 2021 Oct 1;12(5):1911-1929. DOI: 10.1093/advances/nmab033.

[29] van Hunsel F, Scholl J, Vrolijk M, Ekhart C. Impact of Regulatory Action on Dose Maximalization for Vitamin B6 Dietary Supplements on the Reporting Pattern for Neuropathy. Pharmacoepidemiol. Drug Saf. 2025 Feb;34(2):e70108. DOI: 10.1002/pds.70108.

of food supplements containing vitamin B6, of which 100 cases reported taking a dose of less than 21 mg/day and 79 cases reported taking a daily dose of 12 mg or less.[30]

Limitations of spontaneous adverse events reporting

While spontaneous adverse event reporting systems are foundational to global safety surveillance, under-reporting is a major drawback in their capacity to detect safety signals. Multiple factors such as uncertainty around the potential causal relationship and lack of awareness of association for lesser-known medicines such as complementary medicines contribute to under-reporting.[31] Under-reporting is likely further exacerbated for Australian complementary medicines, where patients, when questioned on their medication history, may not disclose use to their treating healthcare professional.[32]

Another significant factor that may lead to under-reporting for complementary medicines is the general perception of safety. Observations from the narratives of vitamin B6 neuropathy cases in DAEN identified that consumers were surprised to find that vitamin supplementation can cause such harm. Current reporting suggests that testing for vitamin B6 toxicity for neuropathy symptoms may be increasing due to increased awareness by health care professionals of the issue. The true rate of occurrence of an adverse event cannot be determined from spontaneous adverse event reporting systems due to both general under-reporting and a lack of usage data. A low number of spontaneous adverse event reports cannot be considered evidence of the absence a safety issue.

While there is variability in the reporting of peripheral neuropathy adverse events, a substantial concern is that for some consumers, the symptoms can be irreversible. Overall, I am convinced that vitamin B6 poses a real risk of peripheral neuropathy to consumers at doses lower than 200 mg/day.

Estimating vitamin B6 intake from multiple sources

The use of vitamin B6 as an ingredient in medicines and supplements is pervasive and the vitamin B6 market in Australia is growing due to its increasing incorporation in dietary supplements, fortified foods, and pharmaceuticals.[33] Currently there are more than 1,500 preparations on the Australian Register of Therapeutic Goods (ARTG) that contain vitamin B6 as an active ingredient. Doses used in the commonly available vitamin B6 preparations are often far higher than the physiological range or the level required in the diet. Currently, preparations providing up to 200 mg of pyridoxine, pyridoxal or pyridoxamine per RDD are available for self-selection without any professional guidance or oversight. Almost 80% of these products provide a dose of more than 2 mg/day, which is above the RDI for pyridoxine, pyridoxal or pyridoxamine.

Due to the widespread addition of vitamin B6 to various products, estimating the total daily vitamin B6 intake from the combination of diet, medicines, supplements and fortified food and beverages, is likely to be beyond the health literacy capability of the typical consumer.

To estimate the total vitamin B6 intake, a consumer is required to:

- know each of the products used that contain vitamin B6 including all the forms that are captured under the term
- know the frequency they are taking each source of vitamin B6
- consider the duration for which they have been taking each of these products, with many supplements advised for long-term use
- then calculate an overall daily vitamin B6 intake.

[30] Nerve damage due to the use of nutritional supplements with vitamin B6. The Netherlands Pharmacovigilance Centre Lareb New Update (13 November 2024), accessed on 23 June 2025.

[31] Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, Lista RM, Staltari O, Scuteri A, Scicchitano F, Russo E. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S66-72. DOI: 10.4103/0976-500X.120955.

[32] Harnett JE, McIntyre E, Steel A, Foley H, Sibbritt D, Adams J. Use of complementary medicine products: a nationally representative cross-sectional survey of 2019 Australian adults. BMJ Open. 2019 Jul 16;9(7):e024198. DOI: https://doi.org/10.1136/bmjopen-2018-024198.

[33] Australia Pyridoxine Hydrochloride Vitamin B6 Market (2025-2031) Outlook | Revenue, Share, Trends, Industry, Size, Companies, Value, Forecast, Analysis & Growth. 6WResearch. 2022 August. Accessed on 16 June 2025.

Vitamin B6 exists in several forms which can appear on labels with different names. Consumers don't often understand that the different chemical forms may also have varied bioavailability.

Almost all vitamin B6 products on the ARTG contain pyridoxine hydrochloride, PLP or PLP monohydrate, and for Listed medicines can contain up to an equivalent of 100 mg RDD of pyridoxine. While pyridoxine is the mandatory component for all the 3 ingredients, there is no requirement to display the equivalent amount of pyridoxine on labels or the total amount of pyridoxine.

For a consumer to accurately determine their vitamin B6 intake a calculation is required to convert pyridoxine hydrochloride, PLP and PLP monohydrate to their pyridoxine equivalents. While the majority of the vitamin B6 listed medicines contain any one of pyridoxine hydrochloride, PLP and PLP monohydrate, currently 80 vitamin B6 medications contain 2 or more of these active ingredients which complicates the estimation of the total vitamin B6 in these products. Overall, the quantity of pyridoxine, pyridoxal or pyridoxamine displayed on the label will be an overestimate of the equivalent pyridoxine intake.

As inclusion of vitamin B6 in products is so widespread, consumers can easily and unknowingly increase their vitamin B6 intake through the use of multiple supplements. A typical example is the daily use of a multivitamin tablet and a zinc or magnesium supplement which both contain vitamin B6. In addition, various food and beverages supplemented with vitamin B6 should also be taken into consideration when estimating a person's total vitamin B6 intake.

Consumers may not understand that combining multiple vitamin B6 containing supplements, or taking high dose individual supplements, in combination with other dietary sources, can quickly lead to high levels of vitamin B6 in the body.

Presentation and warning labels for vitamin B6 containing medicines

Since 1 March 2022, listed medicines containing more than 10 mg per RDD of pyridoxine require a warning statement on the label – *Stop taking this medication if you experience tingling, burning or numbness and see your healthcare practitioner as soon as possible*.

Of concern is that there are several products on the market where the front of the label provides no indication that vitamin B6 is an ingredient, and consumers may believe that the product is a single ingredient preparation. A consumer would not know that vitamin B6 is present unless they read the ingredient panel and, in some circumstances, need to know that pyridoxine (or pyridoxine hydrochloride), pyridoxal and pyridoxamine are forms of vitamin B6.

The evidence for the effectiveness of labels in raising consumer awareness of the potential risks from the use of complementary medicines is equivocal. Relying on labelling alone to manage potential risks also puts additional responsibilities on consumers. Many consumers do not regularly read complementary medicine labels or understand the information they read on those labels.[34] A recent Australian study of 125 complementary medicine users reported that after reading the warning statements less than 50% (61 participants, 48.8%) sought further information on the product before using it.[35] Notably, 61 participants (48.8%) were not concerned by the warnings and 13 (10.4%) admitted to not reading the labels. This study also reported that the internet is the main source of information for users of complementary medicines. Another study also reported dietary supplement users often use the internet to seek information and rarely consult a health-care professional.[36]

These are small cohort studies, and the conclusions have limitations when extrapolating to the general population. I agree with the authors regarding the need for larger studies to understand the usage, effectiveness and appropriateness of labels on complementary medicines.

[34] Boon H, Bozinovski N. A Systematic Narrative Review of the Evidence for Labeling of Natural Health Products and Dietary Supplements. J Altern Complement Med. 2019 Aug;25(8):777-788. DOI: 10.1089/acm.2018.0533.

[35] Naseri K, Thrimawithana T, Allahham A, Nooney V, de Courten B, Shahin W. Exploring Complementary Medicine Usage, Consumer Perceptions, and Impact of Label Warnings: A Cross-Sectional Study in Melbourne, Australia. Pharmacy (Basel). 2025 Apr 27;13(3):61. DOI: 10.3390/pharmacy13030061.

[36] Nathan JP, Kudadjie-Gyamfi E, Halberstam L, Wright JT. Consumers' Information-Seeking Behaviors on Dietary Supplements. Int Q Community Health Educ. 2020 Apr;40(3):171-176. DOI: 10.1177/0272684X19874967.

Conclusion

I have decided to amend the scheduling of vitamin B6 to restrict the access to medicines providing more than 50 mg per RDD of vitamin B6 by classifying these as Pharmacist Only Medicines (Schedule 3).

This interim decision balances the:

- limited benefits of vitamin B6 when considering dietary availability and the rareness of clinical deficiency
- extensive use of vitamin B6 in listed medicines and fortified foods and beverages
- margin of safety between therapeutic and toxic doses in conjunction with the wide inter-individual variability in the metabolism of vitamin B6
- risks of peripheral neuropathy, including irreversible adverse effects
- uncertainties regarding the overall daily intake of consumers using supplements
- burden on consumers to calculate their total daily intake of vitamin B6.

The daily requirement of vitamin B6 can be easily obtained from the usual Australian diet, and the use of supplemental vitamin B6 provides limited benefit except in people who have a clinically diagnosed vitamin B6 deficiency. In contrast, high intake of vitamin B6 poses a risk of peripheral neuropathy, which cannot be excluded for doses less than 50 mg/day. Under the current labelling requirements, it is difficult for a consumer to estimate their vitamin B6 intake and the widespread presence of vitamin B6 in listed medicines and food supplements makes it more challenging. Paradoxically, the most common symptoms associated with vitamin B6 toxicity are similar to those of vitamin B6 deficiency. Therefore, it is possible that consumers may inadvertently exacerbate the very symptoms they are trying to treat. In addition, inter-individual variability in metabolism makes it difficult for individuals to know whether the vitamin B6 products they take may pose a risk.

Turning my mind to scheduling factors 1, 3 and 5 of Schedule 3, a pharmacist-consumer consultation can significantly help consumers in safe use of these supplements, including the difficulties of consumers determining their daily dosage, and reduce the risks from overuse, including potentially irreversible peripheral neuropathy. The benefits of involving a health-care professional in the decision to take dietary supplements should be encouraged where there are associated risks from use. Several European regulatory agencies advise taking no more than 10 mg/day of vitamin B6 except under medical advice.[37, 38]

Although there is poor evidence of a benefit for dietary supplements for most people with a healthy, balanced diet, they are crucial for people with dietary deficiencies or at-risk populations. Medicines providing higher doses of vitamin B6 (in excess of 200 mg per RDD) will therefore continue to be available as Prescription Only Medicines (Schedule 4).

In deciding 50 mg as the cut-off for exemption from scheduling, rather than the 5 mg proposed by the applicant, I have also considered the Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes established by the National Health and Medical Research Council (NHMRC). The NHMRC established an upper level of intake for adults 19 years and over at 50 mg/day. Decreasing the limit of unscheduled preparations from 200 mg to 50 mg of vitamin B6 should reduce the risks from use of a single product, and from combined exposure from multiple sources.

Internationally, the acceptable level set by other regulatory bodies varies considerably and ranges from 10 mg/day in the UK[39] to 100 mg/day in Canada[40] and the USA.[41] Food Standards Australia New Zealand (FSANZ) reviewed the UL set by various international agencies and considered the UL of 25 mg/day for adults set by the EU to be the most relevant because it was derived from longer-term

[37] Vitamin B6 - pyridoxine. Good Standards Scotland. Accessed on 23 June 2025.

[38] B vitamins and folic acid. National Health Service, United Kingdom. Accessed on 23 June 2025.

[39] Safe Upper Levels for Vitamins and Minerals. Report of the United Kingdom Expert Group on Vitamins and Minerals (2003).

[40] Dietary reference intakes tables: Reference values for vitamins. Health Canada. Accessed on 23 June 2025.

[41] Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Institute of Medicine. 1998. Washington, DC: The National Academies Press. DOI: 10.17226/6015.

studies in humans.[42] The EFSA Panel on Nutrition, Novel Foods and Food Allergens recently has set an UL of 12.5 mg/day for vitamin B6.[27] While there are reports of vitamin B6 related neuropathy at doses less than 50 mg/day, the numbers are limited and the evidence is equivocal as to the causal link between vitamin B6 intake at these lower consumed doses and the development of neuropathy symptoms.[43]

I note that in 2018, regulatory changes in the Netherlands to lower the maximum daily dose for vitamin B6 to 21 mg/day resulted in a decrease in daily dose of vitamin B6 and adverse reports of neuropathy.[44] However, cases describing neuropathy related to vitamin B6 supplementation were still reported in the Netherlands in 2023.

Recommendations for other actions to complement the Interim Decision

Scheduling is only one part of the regulatory framework for managing risks from the use of medicines. The scheduling for pyridoxine, pyridoxal and pyridoxamine intersects with other regulatory controls which should be reviewed in consideration of this Interim Decision.

Following the public consultation on this Interim Decision and depending on the Final Decision, I recommend that the Delegates responsible for the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 and the Therapeutic Goods (Medicines Advisory Statements) Specification 2021 review the appropriateness of the pyridoxine, pyridoxal and pyridoxamine entries to address conflicting requirements.

Currently, the Permissible Ingredient Determination allows up to 100 mg of pyridoxine per RDD in listed medicines for individuals aged 19 years and older. Products which contain pyridoxine between 100 and 200 mg are considered registered complementary medicines.

If this Interim Decision is made final, I recommend that these instruments be reviewed to:

- require all forms to include the term vitamin B6 in the ingredient list; for example, vitamin B6 (pyridoxine hydrochloride).[45]
- consider whether ingredient labels should also express the amount of vitamin B6 present (in pyridoxine equivalents) and provide the total amount of vitamin B6 in the case of medicines containing more than one vitamin
- consider a limit on the duration of use
- simplify and strengthen the warnings; for example,
    - Excess consumption of vitamin B6 can cause nerve damage. Stop use and see a doctor if you experience tingling, burning or numbness. OR
    - Stop use and see a doctor if you experience tingling, burning or numbness [contains vitamin B6].
- consider the whether the required statements for pyridoxine and pyridoxal in single and multi-ingredient preparations should be aligned.
- consider whether the current threshold of 10 mg per RDD for requiring warning statements should be reduced to a level closer to the recommended dietary intake (e.g. 2 mg).

The majority of consumers who use complementary medicines perceive these medicines to be safe and effective.[35] However, each individual medicine and its formulation is not assessed by the TGA. Instead, listed medicines can only use ingredients that the TGA has assessed for safety and quality.

Due to consumer behaviour which is weighted toward a positive perception of the benefits of complementary medicines compared with the potential risks and importance of instruction and warning labels, I support the Committee's recommend of an education campaign to raise consumer knowledge

[42] Attachment 6 (Nutrition Assessment) to the Food Standards Australia New Zealand Final Assessment Report in relation to an application to permit addition of addition of vitamins and minerals to formulated beverages, 2005. Accessed on 23 June 2025.
[43] van Hunsel F, van de Koppel S, van Puijenbroek E, Kant A. Vitamin B_6 in Health Supplements and Neuropathy: Case Series Assessment of Spontaneously Reported Cases. Drug Saf. 2018 Sep;41(9):859-869. DOI: 10.1007/s40264-018-0664-0.
[44] van Hunsel F, Scholl J, Vrolijk M, Ekhart C. Impact of Regulatory Action on Dose Maximalization for Vitamin B6 Dietary Supplements on the Reporting Pattern for Neuropathy. Pharmacoepidemiol Drug Saf. 2025 Feb;34(2):e70108. DOI: 10.1002/pds.70108.
[45] Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines may also need to be reviewed in conjunction with the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 and the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.

and awareness of the risks from overuse of vitamin B6. However, large-scale education campaigns are outside the purview of scheduling. I note that the TGA recently ran a public awareness campaign on understanding complementary medicines, educating consumers on how complementary medicines might interact with other medicines (www.tga.gov.au/news/blog/understanding-complementary-medicines). I also note that the NPS Medicinewise website (www.nps.org.au), which contains limited consumer information on the safe use of complementary medicines is currently under review by the Australian Commission on Safety and Quality in Health Care.

I strongly encourage the complementary and alternative medicines industry, particularly the sponsors of vitamin B6 medicines, to initiate and support such educational activities.

I also suggest that FSANZ consider the appropriateness of the 10 mg limit for vitamin B6 in formulated caffeinated beverages (colloquially known as energy drinks) considering the risks from the use of multiple products containing vitamin B6.

Implementation considerations

The scheduling changes will impact more than 100 preparations currently listed in the ARTG that provide more than 50 mg per RDD of vitamin B6 (excludes medicines containing vitamin B6 in combination with other active ingredients such as multivitamins) which accounts for 7% of the vitamin B6 only preparations.

Consequently, sponsors of these preparations will need to decide whether to continue marketing these products, reformulate the level of vitamin B6 to be 50 mg or below, or phase them out of the market. Any products that continue to include vitamin B6 between 50-200 mg will need to be evaluated as a registered medicine. Studies on the efficacy and reformulation of some these products may also be required. I have therefore decided on an implementation period of 18 months. This will also allow the TGA to review the other regulatory controls currently in place for vitamin B6 preparations and aim to align the timeline for any other changes.

Proposed implementation date

1 February 2027.

Therapeutic Goods Administration

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

Web: tga.gov.au