Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Proposed changes to requirements for listed medicine ingredients: Annual low-negligible risk changes 2022-2023

Consultation paper

Version 1.0, August 2022

TGA Health Safety Regulation

Contents

Introduction

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

Purpose

The proposed ingredient changes in this consultation have been reviewed and categorised as being of low-negligible risk. The purpose of this consultation is to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes, which are proposed to commence on **1 March 2023** (see schedule for low-negligible risk changes for 2022-2023). Sponsors will be provided with a 12-month transition period from the commencement of the Determination to align their products with these changes.

Transition expectations

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

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

Proposed changes to requirements for listed medicine ingredients

1. Warning statement requiring healthcare professional supervision for the ingredients *Chelidonium majus* and *Larrea tridentata*

Background

The ingredients *Chelidonium majus* (also known as Greater celandine) and *Larrea tridentata* (also known as Chaparral) can only be included in listed medicines when a label warning statement is present specifying that the medicine is to be used "only under the supervision of a healthcare professional". This requirement is intended to address the risk of hepatotoxicity associated with this ingredient. However, the expectation that consumers must seek supervision from a healthcare professional to use a listed medicine is incongruous with the low-risk framework for listed medicines, which are intended to be available for self-selection and accessible to consumers at supermarkets, health food shops and other retailers.

The TGA sought advice from the Advisory Committee on Complementary Medicines (ACCM) on this issue at the 28th meeting in July 2021. Members concluded that the warning statement 'Use only under the supervision of a healthcare professional' is incongruous with the listed medicines framework. It was suggested that ingredients with this warning may remain in the Permissible Ingredients Determination if the warning statement is changed, acknowledging that the identified risk must continue to be mitigated by a new warning. However, if the ingredient presents a risk to consumers which is unacceptable without the supervision of a healthcare professional, then a recommendation for scheduling in the Poisons Standard should be considered. Members acknowledged that scheduling an ingredient and removing it from the Permissible Ingredients Determination may limit availability of that ingredient for consumers.

Between 1999 and 2022 the TGA received 8 liver-related adverse event reports associated with the consumption of products containing *Chelidonium majus* and 2 reports of liver related adverse events associated with the consumption of products containing *Larrea tridentata*, however it is noted there are very few listed medicines that currently contain these ingredients. Liver injury associated with *Chelidonium majus* and *Larrea tridentata* have also been the subject of scientific publications (Ballotin et al., 2021; Kotsiou & Christine, 2017; Teschke, et al., 2012; Licata, et al., 2013; Stickel, et al., 2005; Arteaga et al., 2005; NIH LiverTox, 2022a; NIH LiverTox, 2022b).

Warning statement

The current warning statements were introduced in 2005 at the recommendation of the Complementary Medicines Evaluation Committee (CMEC) in response to a safety review conducted by the TGA. A similar warning statement is listed in the Required Advisory Statements for Medicine Labels (RASML). However, RASML does not apply to listed medicines, and changes to RASML are outside the scope of this consultation. The warning statement in RASML will be reviewed at a later date.

The TGA proposes to update these warning statements. Given that both *Chelidonium majus* and *Larrea tridentata* have identical warning statements, it is proposed that both statements are amended for consistency, in line with the ACCM recommendation. The proposed warning statement will inform consumers of the symptoms of liver damage and direct them to cease intake of the medicine to reduce the risk of severe outcomes. The warning statement will also

direct the consumer to specifically see a doctor (rather than any healthcare professional). This is to ensure that liver damage can be accurately diagnosed, and management and treatment initiated immediately if required.

Additionally, it is proposed that the common names of the ingredients, Greater celandine and Chaparral, be replaced in the warning statement with the appropriate ingredient names specified in the Permissible Ingredients Determination: *Chelidonium majus* and *Larrea tridentata*. This will enhance clarity for consumers and improve consistency between the warning statement, and the ingredients listed on the label of a medicine.

Consultation

The TGA is seeking consultation on an amendment to the requirements of the ingredients below included in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to address the risk of serious liver damage to consumers by recommending cessation of the product when specific symptoms are observed.

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

Affected ingredients

- *Chelidonium majus*
- *Larrea tridentata*

As of 20 July 2022, there were 4 listed medicines on the ARTG containing *Chelidonium majus*, and 0 listed medicines containing *Larrea tridentata.*

Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
CHELIDONIUM MAJUS	When for oral or sublingual use, the medicine requires the following warning statement on the medicine label: - (CELAND) 'WARNING: Greater Celandine may harm the liver in some people. Use only under the supervision of a healthcare professional'.	When the medicine is for oral or sublingual use, ~~the medicine requires~~ the following warning statement is required on the medicine label: ~~- (CELAND) 'WARNING: Greater Celandine may harm the liver in some people. Use only under the supervision of a healthcare professional'.~~ 'WARNING: Chelidonium majus may harm the liver in some people. If you experience yellowing of the skin/eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, abdominal pain, and/or loss of appetite, stop using this product and see your doctor.'

Ingredient name	Existing specific requirements	Proposed specific requirements
LARREA TRIDENTATA	The medicine requires the following warning statement on the medicine label: - (CHAP) 'WARNING: Chaparral may harm the liver in some people - use only under supervision of a health care professional'.	The ~~medicine requires the~~ following warning statement is required on the medicine label: ~~- (CHAP) 'WARNING: Chaparral may harm the liver in some people - use only under supervision of a health care professional'.~~ 'WARNING: Larrea tridentata may harm the liver in some people. If you experience yellowing of the skin/eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, abdominal pain, and/or loss of appetite, stop using this product and see your doctor.'

2. Liver injury associated with *Valeriana officinalis*

Background

Valeriana officinalis ('valerian') is commonly used as a medicinal herb in Australia for multiple indications including as a sleep aid and for digestive and urinary problems. It is currently permitted for use in listed medicines with no restrictions on dose, concentration, or type of preparation, and no label warnings are currently required in relation to this ingredient.

Adverse event reports

In February 2019, the TGA received a report of a case of a serious drug-induced liver injury following consumption of valerian, and subsequently initiated an investigation into the potential relationship between valerian and hepatotoxicity. The TGA has previously considered valerian-associated hepatitis in 1999, 2008 and 2016; however, at these times, there was insufficient data to warrant action to be taken.

Between 1983 and 2021, the TGA received 16 Australian reports of liver injury in consumers taking products containing valerian. Ten of these cases involved products containing other active ingredients with a known association with liver injury, however, 3 cases involved other active ingredients with no known association with liver injury, and in 3 cases, valerian was the only reported active ingredient in the single suspected medicine. While most cases of liver damage resolved after the use of the valerian product was discontinued, 4 cases showed markers of severe liver injury, 3 of which reported hospitalisation. Two of these severe cases involved valerian as the single suspected ingredient/medicine, while the other 2 involved co-suspected herbal ingredients not associated with liver injury.

The TGA located 15 published literature cases of liver injury associated with valerian that occurred internationally, 5 of which involved valerian as the sole suspected ingredient, with 2 of these 5 cases reporting hospitalisation (Kulkarni, et al., 2017; Lourdusamy, et al., 2019; Cohen & Del Toro, 2008; Garcia-Cortes, et al., 2008; Tomeny et al., 2018; Vassiliadis, et al., 2009). The TGA also located 57 cases of drug related liver adverse events associated with valerian reported internationally by overseas regulatory authorities, including 27 with valerian as the single suspected medicine.

Where reported, cases involved a variety of dosages, and oral dosage forms including tablets, capsules, extracts and teas. These cases reported both short term and extended treatment durations of valerian. While details regarding preparation types, dose and duration of use were limited for many cases, the available information suggests valerian associated liver injury is idiosyncratic. No trends were observed to indicate intrinsic/predictable liver injury related to dose or duration of use. At this stage the mechanism of hepatotoxicity is unknown. The United States National Institutes of Health (NIH) LiverTox publication considers valerian a probable rare cause of clinically apparent liver injury.

Warning statement

The TGA sought advice on this issue from the Advisory Committee on Complementary Medicines (ACCM) at their 25th meeting in July 2020. Members agreed that despite the low likelihood of adverse events, the severity was serious enough to warrant the implementation of risk mitigation. Consequently, the TGA published a safety advisory notice on the TGA website in October 2020, notifying consumers and health professionals of the risk of liver injury associated with the consumption of valerian. ACCM also recommended that a label warning statement be required on products containing valerian, consistent with other warning statements required for ingredients associated with a risk of serious liver injury.

The widespread and potential long-term use of valerian warrants implementation of risk mitigation strategies for liver related adverse events resulting from oral valerian use.

Based on the adverse event reports, the severity of liver injury may be reduced by ceasing intake of the medicine and seeking medical attention as soon as symptoms are noticed. The TGA proposes a warning statement to increase consumer awareness of the risk of liver injury associated with valerian, and to inform the consumer of symptoms of liver injury and advise seeing a doctor if those symptoms are observed. Given that the adverse events described above were only observed for oral dosage forms of valerian, the warning statement is only proposed for oral use. This ensures that listed medicines containing valerian remain safe for self-selection and administration and aligns with the recommendation provided by ACCM.

For consistency between valerian-containing medicines, the warning statement for the 3 valerian-related ingredients included in the Determination is proposed to specify the common name 'Valerian'. It is not anticipated that use of Valerian on the medicine label will introduce consumer confusion, due to the obvious similarity with the ingredient names *Valeriana officinalis,* valerian dry, and valerian powder.

Consultation

The TGA is seeking consultation on an amendment to the requirements of the below affected ingredients in the Therapeutic Goods (Permissible Ingredients) Determination. The proposed specific requirements below are intended to reduce the risk of serious liver damage to consumers by recommending cessation of the product and consultation with a doctor when specific symptoms are observed.

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

Affected ingredients

- VALERIAN DRY
- VALERIAN POWDER
- VALERIANA OFFICINALIS

As of 18 July 2022, there were 101 listed medicines included in the ARTG containing at least one of these ingredients. These include 96 medicines for oral use.

Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
VALERIAN DRY		The following warning statement is required on the medicine label when the medicine is for oral use: 'WARNING: Valerian may harm the liver in some people. If you experience yellowing of the skin/eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, abdominal pain, and/or loss of appetite, stop using this product and see your doctor.'
VALERIAN POWDER		The following warning statement is required on the medicine label when the medicine is for oral use: 'WARNING: Valerian may harm the liver in some people. If you experience yellowing of the skin/eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, abdominal pain, and/or loss of appetite, stop using this product and see your doctor.'
VALERIANA OFFICINALIS		The following warning statement is required on the medicine label when the medicine is for oral use: 'WARNING: Valerian may harm the liver in some people. If you experience yellowing of the skin/eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, abdominal pain, and/or loss of appetite, stop using this product and see your doctor.'

Making a submission

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

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

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

Privacy and your personal information

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

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

The TGA may disclose your name, work title, company, and submission on the Internet (i.e. make this information publicly available) with your consent. You may specify whether there is anything in your submission which you would prefer to not be published online (e.g. names, email addresses, proprietary information) by:

- Providing an additional, redacted copy of your submission; or
- Providing details of content not to be published e.g. “Do not publish pages 3-5”, “Please redact contact details”; or
- Identifying any text within your submission to remain confidential by having it clearly marked 'IN CONFIDENCE' and highlighted in grey.

Please do not include personal information about other individuals in the body of your submission. Personal information in this context means information or an opinion about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion. The TGA will not publish personal information about you/others without your/their consent unless authorised or required by law.

Timetable

This consultation opened on **Thursday 4 August 2022.**

Interested parties should respond by close of business **Thursday 15 September 2022.** Please note that late submissions after this date may not be considered.

Following consideration of public submissions, outcomes of these proposals will be published to the Consultation Hub web page by **Thursday 1 December 2022.**

The confirmed changes to the Determination will commence on **Wednesday 1 March 2023**.

The transition period of 1 year will end on **Friday 1 March 2024** 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.

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Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary Medicines Evaluation Section	4 August 2022

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Reference/Publication D22-5610042