Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Proposed changes to requirements for listed medicine ingredients: Annual low-negligible risk changes 2024-25

Final Decisions

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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 to ingredients were presented for consultation after they were reviewed and categorised as being of low-negligible risk. Ingredients are classified low-negligible risk where a delay to implementation of a change to an ingredient is not likely to pose an imminent or serious safety risk to consumers. 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.

Public consultation

The consultation opened on **2 August 2024** and closed on **13 September 2024**.

The consultation document can be accessed here.

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

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 Submissions received with claims of confidentiality or privacy have been redacted or remain unpublished as specified by the submitter.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 described in this Final decisions document will commence on **1 March 2025**, and will include a 12-month transition period until **1 March 2026** (see schedule for low-negligible risk changes for 2024-2025), with exception for changes relating to Australian Approved Names (AANs).

Transition periods provide sponsors of existing listed medicines with time to make the necessary arrangements to bring their products into compliance. Sponsors should ensure that no product is **released for supply** after the expiry of the transition period, unless that product (including the details in the Australian Register of Therapeutic Goods [ARTG] listing) is compliant with any new applicable requirements. After the expiry of the transition period, any ARTG listings or products **released for supply** that do not comply with the new requirements may be targeted for review.

Transition provisions for sponsors changes relating to AANs will be arranged via consent to supply therapeutic goods that do not conform with a standard for a specified period.

Proposed changes to requirements for listed medicine ingredients

1. Herbal ingredients with pregnancy contraindications and other toxic effects

1.1 *Ruta graveolens* (Common Rue)

Background

The consultation document discussed the evidence regarding *Ruta graveolens* (Common Rue) with concerns related to use in pregnancy, specifically traditional use as an abortifacient and emmenagogue, as well as concerns regarding phototoxicity. It was proposed that all medicines containing *Ruta graveolens*/rue oil include a pregnancy warning statement on the product label, as well as limiting the availability of these ingredients to homoeopathic medicines.

We are aware of a general consumer perception that herbal medicines are thought to be safer than conventional medicines. This perception can extend to use during pregnancy.

Consultation submissions

Six submissions were received in response to this proposal.

Two submissions from relevant clinical professional organisations (e.g. representing clinical practitioners and pharmacists) fully supported the introduction of pregnancy warning statements for these ingredients. Four industry representatives supported or did not object to the addition of a pregnancy warning, however they opposed the removal of active and/or excipient availability and suggested alternative approaches to managing the safety concerns.

TGA response

As discussed in the consultation paper, the TGA acknowledges that *Ruta graveolens* (*R. graveolens*) is used both topically and orally in medicines for a wide range of indications, and along with its essential oil (rue oil) has been used as a flavouring agent in foods and beverages and as a fragrance in soaps and cosmetics. In light of the risks in pregnancy and phototoxicity based on the information the TGA has on hand, risk mitigation steps need to be taken to ensure the ingredients are safe in medicines that are available for self-selection. Further, the dose at which *R. graveolens* does not present a risk to pregnancy is unclear from traditional literature and there appears to be a wide variation in the information available. Such challenges can be overcome by increasing awareness of the potential risks among women who are planning to conceive, pregnant and lactating, and healthcare professionals who will be better informed to advise these group of patients.

The TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

Warning statement for those who are pregnant, are likely to become pregnant, or lactating

All of the submitted responses supported, or did not object to, the introduction of a warning label on medicines containing *R. graveolens* and rue oil advising consumers not to use if pregnant, or likely to become pregnant, or during lactation.

Two responses from clinical professionals representing pharmacists and practitioners in women's health are fully supportive of the proposed changes to *R. graveolens* and rue oil. Both respondents approved of complementary medicines bearing clear and consistent labelling requirements. One

respondent acknowledged that the use of complementary medicines may not always be disclosed with the women's pregnancy care provider due to the general consumer perception that complementary medicines are thought to be safer than conventional medicines. The advantages of inclusion of a warning statement are two-fold: to ensure the safety of patients and to empower healthcare professionals to make informed decisions. The two respondents concurred with the TGA that the inclusion of a pregnancy warning statement is warranted, when theoretical concerns are raised.

Opposition to removal of active and excipient use

All industry submissions (four) opposed the TGA proposal to make *R. graveolens* and rue oil available for use only in homoeopathic medicines, citing restriction of the use of the ingredients to current products does not justify the removal of their use as active and excipient ingredients and the cost to industry having this ingredient assessed by the TGA for re-entry on the Determination.

Oral use of *R. graveolens* and rue oil presents regulatory challenges, given their well-documented abortifacient properties, and the lack of consistent and specific data in the available literature regarding the dose, frequency, duration or preparation types that may result in miscarriage or other serious adverse events. As noted in the consultation document, the TGA is unable to determine a safe dose of *R. graveolens* or rue oil for oral use during pregnancy or lactation, and the Advisory Committee on Complementary Medicines (ACCM) recommended that further consideration be given to whether these ingredients were suitable to remain in the Determination. As such, oral use of *R. graveolens* and rue oil will be limited to homoeopathic products, which will align with the products currently listed on the ARTG.

However, two industry submissions noted that homoeopathic preparations containing these ingredients may not pose any safety risk, depending on the dilution level, and thus would not warrant a warning statement. One submission proposed that the pregnancy warning statement be applied only to homoeopathic potencies of 12X or 6C or less dilute, based on the homoeopathic principles that result in more dilute preparations being unlikely to include a single molecule of the original substance. The TGA accepts that highly diluted homoeopathic products for oral and topical for dermal use would be unlikely to pose a risk to consumers and therefore a warning statement will not be necessary for preparations containing homoeopathic potencies more dilute than 12X.

Topical use

Two respondents representing industry cited references documenting the history of traditional topical use of *R. graveolens* for the treatment of wounds and the relief of inflammation, bruising and rheumatic aches pains[1], stemming from its antispasmodic, antitussive and antimicrobial properties[2]. The TGA acknowledges the benefits of the topical use of these ingredients, however, in the absence of robust scientific studies such as dermal absorption studies, the TGA is unable to discern the margin of exposure for which *R. graveolens* and rue oil are safe when used in topical listed medicines as active and excipient ingredients.

One respondent raised concerns that the adverse events reported were confounded by multiple-ingredient formulations. As discussed in the consultation paper, a review of the WHO VigiBase data revealed 11 cases involving single ingredient medicines that contained *R. graveolens*, with 5 of these reporting it as the sole suspected medicine. One case resulted in fatality of an infant after topical application to the infant's skin, while another of phototoxicity after topical use. As such, there are inherent risks related to the topical use of *R. graveolens*.

One industry respondent contended that rue oil can be used as fragrance at low concentrations for dermal products and cited the International Fragrance Association (IFRA) standard for rue oil limits dermal use to a maximum level of 0.15%[3] regarding the phototoxicity potential of furocoumarins present in the essential oil. Without absorption studies, the TGA considers this an acceptable cut-off for *Ruta graveolens* and rue oil in topical products when used as excipient for dermal application, specifically when used as a fragrance component in proprietary formulations to mitigate the risk of phototoxicity.

On this basis, the TGA elects to expand the use of rue oil for excipient use in topical preparations as fragrance in proprietary formulations, and that restriction of a maximum acceptable concentration of 0.15% will ensure the ingredient is safe. In line with acceptable flavour proprietary ingredient limits, the total concentration of fragrance proprietary excipient formulations containing rue oil will be limited to 1% in listed medicines. *R. graveolens* will also be restricted to excipient use with the same conditions applied to rue oil as above.

In the absence of robust scientific data, the TGA considers the inherent risks of use of both *R. graveolens* and rue oil outweigh their benefits, when used as active ingredients in listed medicines, regardless of routes of administration. The decision is to restrict the active use of both ingredients to homoeopathic preparations only, where exposure is significantly reduced.

Risk of phototoxicity

Two industry submissions also recommended additional warning statements for dermal products to mitigate the risk of phototoxicity, advising consumers to avoid prolonged exposure to sunlight and that application to skin may increase sensitivity to sunlight. However, as discussed in the consultation paper, recognising that the available evidence regarding phototoxicity largely relates to the use of fresh plant matter, an inclusion of one warning statement is likely to sufficiently mitigate this risk for topical medicines. The TGA has elected to include the warning statement 'Application to skin may increase sensitivity to sunlight' (or words to that effect). An additional statement, advising that the product is for external use only, was also proposed. However, the TGA regards this statement as unnecessary given that the final restrictions are sufficient in limiting the routes of administration of the ingredients. The TGA is cognisant that the lack of product label space concerns consistently raised by the complementary medicines industry.

Warning statement directed at women only

One industry submission raised the option of only applying the warning statement to products directed at women, however the TGA considers this an unnecessary caveat, as current products containing these ingredients are all available to the general population.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA will implement new requirements for *R. graveolens* and rue oil which reflect the feedback received. Specifically, the current availability of the ingredients for active and homoeopathic use will be maintained but restricted to active homoeopathic preparations for oral and topical for dermal use. However, active homoeopathic preparations at homoeopathic potency of 12X or lower will require a warning statement contraindicating use in those who are planning to fall pregnant, are pregnant and lactating. For homeopathic preparations for dermal use, a warning statement advising consumers of the increased sensitivity to sunlight will also be implemented. *R. graveolens* will retain its excipient use, while rue oil will be expanded for excipient use, however, both will be restricted to topical medicines with a 0.15% concentration limit when used as a fragrance in proprietary formulations, where such formulations are limited to 1% of the total medicine.

The TGA will continue to monitor these safety signal sand adverse events related to this issue. The current requirements may be revised in the future if new evidence becomes available to the TGA to support the change.

Affected ingredients

- RUTA GRAVEOLENS
- RUE OIL

Final changes to specific ingredient requirements in the Determination[i]

Ingredient name	Existing availability	Proposed availability	Existing specific requirements	Proposed specific requirements
RUTA GRAVEOLENS	A, E, H	A, E, H	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When used as an active ingredient: (a) Ruta graveolens must only be used as a homoeopathic ingredient; (b) the routes of administration for medicines that contain Ruta graveolens must be limited to: (i) topical for dermal use; and (ii) oral; (c) when the homoeopathic potency of the medicine containing Ruta graveolens is 12X or lower, the following warning statement is required on the medicine label: - (NEW) 'Do not use if pregnant or likely to become pregnant, or during lactation.'; and (d) when the medicine is for dermal use, the following statement is required on the medicine: - (SENS) 'Application to skin may increase sensitivity to sunlight' (or words to that effect). When used as an excipient ingredient: (a) The route of administration for medicines that contain Ruta graveolens must be limited to topical; (b) Ruta graveolens must only be included in combination with other permitted ingredients as a fragrance proprietary excipient formulation; (c) the total concentration of fragrance proprietary excipient formulations containing Ruta graveolens must not be more than 1% of the total medicine; and (d) the total concentration of Ruta graveolens in the medicine must not be more than 0.15%.

[i] Proposed additions are shown in green font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Permissible Ingredients Determination.

Ingredient name	Existing availability	Proposed availability	Existing specific requirements	Proposed specific requirements
RUE OIL	A, H	A, E, H	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When used as an active ingredient: (a) Rue oil must only be used as a homoeopathic ingredient; (b) the routes of administration for medicines that contain rue oil must be limited to: (i) topical for dermal use; and (ii) oral; (c) when the homoeopathic potency of the medicine containing rue oil is 12X or lower, the following warning statement is required on the medicine label: - (NEW) 'Do not use if pregnant or likely to become pregnant, or during lactation.'; and (d) when the medicine is for dermal use, the following statement is required on the medicine: - (SENS) 'Application to skin may increase sensitivity to sunlight' (or words to that effect). When used as an excipient ingredient: (a) The route of administration for medicines that contain rue oil must be limited to topical; (b) rue oil must only be included in combination with other permitted ingredients as a fragrance proprietary excipient formulation; (c) the total concentration of fragrance proprietary excipient formulations containing rue oil must not be more than 1% of the total medicine; and (d) the total concentration of rue oil in the medicine must not be more than 0.15%.

1.2 *Petroselinum crispum* (parsley)

Background

The consultation document discussed evidence related to *Petroselinum crispum* (parsley) and concerns with its use during pregnancy, when used in concentrated amounts in therapeutic goods. It proposed that all medicines containing *P. crispum* and related ingredients include a pregnancy warning statement on the product label. Parsley in food is not regulated by the TGA, however the TGA acknowledges the issue discussed in this paper relates to more concentrated constituents of parsley than that consumed as part of the average human diet, leading to potential safety concerns.

Consultation submissions

Six submissions were received in response to this proposal.

Two submissions from relevant clinical professional organisations (e.g. representing clinical practitioners and pharmacists) fully supported the introduction of pregnancy warning statements for these ingredients.

Three industry representatives supported the proposed pregnancy warnings, with some suggested amendments, however one industry representative strongly opposed the warning statement, due to the lack of recorded adverse events or regulatory controls in other jurisdictions.

TGA response

The TGA thanks stakeholders for their submissions.

Pregnancy warning statement

Two responses from clinical professionals representing pharmacists and practitioners in women's health are fully supportive of the proposed changes to *P. crispum.* One respondent noted that there are no evidence-based indications for parsley use during pregnancy, and traditional uses may induce miscarriage. Consumer perception that herbal medicines are safer may lead to such medicines not being discussed with pregnancy care providers, therefore general label warnings are warranted to increase awareness and protect consumers. Both respondents support clearer label warnings to enable better decision making by healthcare professionals when offering advice to patients.

One industry submission strongly opposed the addition of the warning statement, noting that there are no TGA or WHO reports of adverse events related to pregnancy, and no other jurisdiction requires such a warning. They noted that parsley is a commonly used food and cosmetic ingredient.

The TGA acknowledges that there is limited adverse event data documenting the potential harms of parsley in pregnancy. However, as noted in the consultation paper, there is likely significant under-reporting of miscarriage associated with herbal medicines, due to lack of awareness of the risks and the perception that such products are safer than other medicines, as well as the relatively high background rate of miscarriage. The traditional literature shows that parsley has a long history of use as an abortifacient[4]. Additionally, medicinal preparations of parsley will have a different safety profile from food use, as there is potentially increased risk to components of concern in concentrated extracts and essential oil preparations. Therefore, given parsley's known high content of apiol and myristicin[5], which are reported in the literature to be responsible for these effects[6], the risk is considered sufficient to warrant regulatory action, as recommended by the ACCM. In particular, the Committee noted that the warning statement should apply to both oral and topical use, due to the absorption of essential oils through the skin.

All but one industry response supported the introduction of a pregnancy warning statement for parsley ingredients. Two of the industry submissions noted that this warning would not be relevant for products directed for children or men, such as specific multivitamin supplements. These submissions requested that such products be excluded from the warning requirement, as this would ensure the

warning is more appropriate and relevant to consumers and serve to concurrently reduce 'warning fatigue'. The TGA disagrees with this suggestion, as listed medicines are available for self-selection and self-administration, therefore having a blanket warning statement will mitigate potential risks.

Establishing a cut-off and caveats for the warning statement requirement

Three industry submissions also noted that a dose cut-off to exclude products containing very low doses of parsley ingredients from requiring the warning statement would reduce the impact on industry. One submission noted that parsley can be used as a fragrance or excipient in dermal preparations, and companies may choose to reformulate such products containing very small amounts of parsley, which would increase costs, restrict innovation and impose unnecessary barriers for products that are available overseas. Another submission noted that very low doses of parsley in a medicine would not result in meaningful concentrations of apiol or myristicin in the blood, and therefore would be very unlikely to lead to adverse consequences in pregnancy. These submissions requested that such products be excluded from the warning requirement, as this would ensure the warning is more appropriate and relevant to consumers and reduce 'warning fatigue'.

The TGA acknowledges that there is a lack of robust maternal toxicity studies undertaken using parsley (or its components apiol and myristicin) to clearly establish a suitable cut-off at which risks of abortifacient effects can be mitigated. In the absence of contemporary information made available, the TGA has elected to exclude homoeopathic medicines of homoeopathic potencies more dilute than 12X and medicines containing parsley used as excipients in flavour or fragrance proprietary ingredients from requiring the warning statement, as these medicines contain very low concentrations of parsley and are unlikely to pose a significant risk to pregnancy.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA will amend the entries for parsley ingredients in the Permissible Ingredients Determination to require a warning statement contraindicating use in pregnancy for medicines containing these ingredients, except for products containing very low concentrations of parsley.

The TGA will continue to monitor this safety signal and adverse events related to this issue. The current requirements may be revised in the future if new evidence becomes available to the TGA to support the change.

Affected ingredients

- PARSLEY HERB DRY
- PARSELY HERB OIL
- PARSLEY HERB POWDER
- PARSELY SEED OIL
- PETROSELINUM CRISPUM

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	Proposed specific requirements
PARSLEY HERB DRY	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.' unless when: (a) parsley herb dry is used as an active homoeopathic ingredient at a homoeopathic potency of more than 12X; or (b) parsley herb dry is used as an excipient in a flavour where the total concentration of flavour proprietary excipient formulations containing parsley herb dry must not be more than 5% of the total medicine; or (c) parsley herb dry is used as an excipient in a fragrance where the total concentration of fragrance proprietary excipient formulations containing parsley herb dry must not be more than 1% of the total medicine.
PARSELY HERB OIL	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.' unless when: (a) parsley herb oil is used as an active homoeopathic ingredient at a homoeopathic potency of more than 12X; or (b) parsley herb oil is used as an excipient in a flavour where the total concentration of flavour proprietary excipient formulations containing parsley herb oil must not be more than 5% of the total medicine; or (c) parsley herb oil is used as an excipient in a fragrance where the total concentration of fragrance proprietary excipient formulations containing parsley herb oil must not be more than 1% of the total medicine.

Ingredient name	Existing specific requirements	Proposed specific requirements
PARSLEY HERB POWDER	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.' unless when: (a) parsley herb powder is used as an active homoeopathic ingredient at a homoeopathic potency of more than 12X; or (b) parsley herb powder is used as an excipient in a flavour where the total concentration of flavour proprietary excipient formulations containing parsley herb powder must not be more than 5% of the total medicine; or (c) parsley herb powder is used as an excipient in a fragrance where the total concentration of fragrance proprietary excipient formulations containing parsley herb powder must not be more than 1% of the total medicine.
PARSELY SEED OIL	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.' unless when: (a) parsley seed oil is used as an active homoeopathic ingredient at a homoeopathic potency of more than 12X; or (b) parsley seed oil is used as an excipient in a flavour where the total concentration of a flavour proprietary excipient formulations containing parsley seed oil must not be more than 5% of the total medicine; or (c) parsley seed oil is used as an excipient in a fragrance where the total concentration of fragrance excipient formulations containing parsley seed oil must not be more than 1% of the total medicine.

Ingredient name	Existing specific requirements	Proposed specific requirements
PETROSELINUM CRISPUM	None	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.' unless when: (a) Petroselinum crispum is used as an active homoeopathic ingredient at a homoeopathic potency of more than 12X; or (b) Petroselinum crispum is used as an excipient where the total concentration of flavour proprietary excipient formulations containing Petroselinum crispum must not be more than 5% of the total medicine; or (c) Petroselinum crispum is used as an excipient in a fragrance where the total concentration of fragrance proprietary excipient formulations containing Petroselinum crispum must not be more than 1% of the total medicine.

References – herbal ingredients with pregnancy contraindications

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[5] Dosoky, N. S. & Setzer, W. N. 2021. Maternal reproductive toxicity of some essential oils and their constituents. *International journal of molecular sciences,* 22**,** 2380.

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2. *Garcinia* species, hydroxycitric acid, hydroxycitrate complex and salts, and risk of liver injury

Background

The consultation document discussed the risk of liver injury and proposed introducing a liver warning statement for *Garcinia gummi-gutta* and ingredients that contain hydroxycitric acid (HCA). Additionally, the consultation suggested extending the current restriction, which prohibits directions for use for children, pregnant or lactating women for *Garcinia gummi*-gutta, to other HCA-containing ingredients.

Consultation submissions

Four submissions were received in response to this proposal.

One submission from an industry representative and one clinical professional organisation supported the proposed changes. In contrast, two industry representatives provided mixed support for the proposal.

TGA response

The TGA thanks stakeholders for their submissions. A summary of submissions and key issues raised are discussed below.

Wording of the proposed warning statement

One respondent supported the proposed warning and recognised that risk mitigation is critical to ensure that these ingredients remain low-risk, to allow patients to self-select and self-administer these medicines by meeting labelling requirements that indicate the risk of liver toxicity.

One respondent suggested alterations to the wording of the proposed warning statement, to 'In very rare cases', rather than 'In rare cases', and considered this more appropriately reflected the current risk in Australia. The provided justification included:

- the low number of cases reported for HCA-containing listed medicines in Australia,
- possible confounders, including possible quality issue for products not regulated under the Australian therapeutic goods framework,
- an estimated frequency of hepatic adverse reactions to *Garcinia gummi-gutta* by LiverTox of less than 1 in 10,000 persons[7] (LiverTox 2019).

One respondent did not oppose the proposed label warning, however raised concerns with the discussion and rationale presented to support the introduction of the change. They considered that further work is needed to assess the presence and impact of possible adulterants before any regulatory action is taken.

These submissions suggest that liver injury concerns could be due to quality issues, such as contamination or adulteration.

As stated in the consultation, the TGA 's review was unable to locate sufficient evidence to support that liver injury concerns are due to widespread quality issues. The number of cases reported over several years from different regions with no clear clusters suggests that quality issues are not likely to play a significant role in liver injury concerns for *Garcinia gummi-gutta* and HCA.

The TGA acknowledges that while LiverTox has assigned a likelihood score of B (likely rare cause of clinically apparent liver injury) it also notes that the frequency of hepatic adverse reactions to *Garcinia gummi-gutta* is unknown but likely uncommon, possibly in less than 1 in 10,000 persons. In

accordance with CIOMS frequency categories for adverse events, reactions that occur in less than 1 in 10,000 persons are categorised as very rare. Therefore, based on the LiverTox estimate, the TGA has amended the wording of the warning to 'In very rare cases'[7]. This will be monitored and amended if evidence indicates a higher frequency.

Two respondents raised concerns regarding warning statement duplication on the label where a listed medicine contains more than one ingredient that requires a liver warning.

The TGA agrees that this creates unnecessary duplication therefore has decided to amend the preamble to the Determination to create a new provision such that certain warnings related to liver harm may be stated only once on the label when specified conditions are met.

Adverse event reports

One respondent commented on adverse events associated with Garcinia and related ingredients they identified through a search of the TGA's Database of Adverse Event Notifications (DAEN) in August 2024. The respondent noted just 12 of the 32 reports concerned listed medicines and that there have been no adverse event reports since March 2022 for the 50 medicines currently listed on the ARTG that contain one or more of the affected ingredients.

However, as discussed in the consultation, it is possible that the small number of possible liver injury cases associated with HCA-containing ingredients reported to the TGA is attributable to cases going unreported. Notably, one published literature case resulting in liver transplant that occurred in Australia was not reported to the TGA.

As discussed in the consultation, the true rate of occurrence of an adverse event cannot be determined solely from spontaneous adverse event reporting systems, due to both under-reporting and lack of usage data. The TGA does not consider that a low number of cases reported to the TGA is compelling evidence that liver injury from *Garcinia gummi-gutta*/HCA does not warrant risk mitigation in Australia. Similarly, there is insufficient information to conclude that this safety concern is not relevant to the Australian population and/or Australian products.

Additionally, as discussed in the consultation, the TGA's literature review identified that the number of published studies with causality assessment provides a strong body of evidence supporting the safety concern.

Indications for use in pregnant or lactating women

The TGA notes one respondent's suggestion to mandate specific warning statements on the product label for *Garcinia gummi-gutta* and other HCA-containing ingredients as a precautionary alternative to disallowing indications for use in pregnant or lactating women. As discussed in the consultation, there is continued absence of evidence of safe use in pregnant or lactating women.

Accordingly, the TGA considers that the restriction to not permit indications for use of *Garcinia gummi-gutta* and other HCA-containing ingredients in pregnant or lactating women is commensurate with the available evidence. This only affects any products directing use specifically to these population groups. However, we will continue to monitor this issue and consider if further regulatory actions are required. The current requirements may be revised in the future if evidence becomes available to the TGA to support the change.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA will implement new requirements for *Garcinia gummi-gutta* and other HCA-containing ingredients as presented for consultation with minor amendments to replace 'rare' with 'very rare'. Provisions will be made through the preamble of the Determination to permit combined liver-related warnings for multiple ingredients where a similar warning is required for more than one ingredient in a medicine.

With respect to *Garcinia gummi-gutta* the plant part will be changed from 'rind of the fruit' to 'fruit peel' to align with the plant parts in the TGA Code Tables, and that the definition of 'fruit peel' includes the exocarp and the mesocarp of the fruit, which is synonymous with the term 'fruit rind'. Additionally, there will be minor formatting changes for the purpose of improving the internal consistency of the Determination.

The TGA will continue to monitor this safety issue and adverse events related to this issue. The current requirements may be revised in the future if new evidence becomes available to the TGA to support the change.

Affected ingredients

- CALCIUM HYDROXYCITRATE
- GARCINIA GUMMI-GUTTA
- GARCINIA QUAESITA
- HYDROXYCITRATE COMPLEX
- HYDROXYCITRIC ACID
- POTASSIUM HYDROXYCITRATE
- SODIUM HYDROXYCITRATE

Other ingredients affected by amendments to the preamble to the Determination

- CAMELLIA SINENSIS
- CHELIDONIUM MAJUS
- CURCUMA AROMATICA
- CURCUMA LONGA
- CURCUMA ZANTHORRHIZA
- CURCUMA ZEDOARIA
- CURCUMIN
- LARREA TRIDENTATA
- VALERIAN DRY
- VALERIAN POWDER
- VALERIANA OFFICINALIS

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	Proposed specific requirements
CALCIUM HYDROXYCITRATE	-	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, calcium hydroxycitrate may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' Medicines containing calcium hydroxycitrate must not be directed for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
GARCINIA GUMMI-GUTTA	Only for use in oral medicines. Must be obtained from the rind of the fruit only. Must not contain any directions for use for children or pregnant or lactating women.	The requirements specified in paragraphs (a) to (c) below applies to a medicine that contains the ingredient that is: - listed in the Register before 1 March 2025; and - released for supply before 1 March 2026: (a) Only for use in oral medicines. (b) Must be obtained from the rind of the fruit only. (c) Must not contain any directions for use for children or pregnant or lactating women. The requirements specified in paragraphs (d) to (g) below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. (d) The route of administration for medicines that contain Garcinia gummi-gutta must be limited to oral. (e) The plant part must be limited to fruit peel. (f) The following warning statement is required on the medicine label: 'In very rare cases, Garcinia gummi-gutta may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' (g) Medicines containing Garcinia gummi-gutta must not be directed for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
GARCINIA QUAESITA	-	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, Garcinia quaesita may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' Medicines containing Garcinia quaesita must not be directed for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
HYDROXYCITRATE COMPLEX	Hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid.	The requirements specified in paragraph (a) below applies to a medicine that contains the ingredient that is: - listed in the Register before 1 March 2025; and - released for supply before 1 March 2026: (a) Hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid. The requirements specified in paragraphs (b) to (d) below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. (b) Hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid. (c) When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, hydroxycitrate complex may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' (d) Medicines containing hydroxycitrate complex must not be directed for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
HYDROXYCITRIC ACID	-	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, hydroxycitric acid may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' Medicines containing hydroxycitric acid must not be directed for use in children, or in pregnant or lactating women.
POTASSIUM HYDROXYCITRATE	-	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, potassium hydroxycitrate may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' Medicines containing potassium hydroxycitrate must not be directed for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
SODIUM HYDROXYCITRATE	-	The requirements specified below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. When for oral use, the following warning statement is required on the medicine label: 'In very rare cases, sodium hydroxycitrate may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' Medicines containing sodium hydroxycitrate must not be directed for use in children, or in pregnant or lactating women.

References - Garcinia gummi-gutta, Garcinia quaesita, hydroxycitric acid

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3. *Xanthium* species

Background

The consultation document proposed to remove *Xanthium strumarium* and *Xanthium sibiricum* (collectively '*Xanthium* spp.') from the Determination due to multiple reports of toxicity associated with consumption of *Xanthium* plants or medicinal products containing *Xanthium* species. The toxicity is attributed to the presence of atractyloside (ATR) and carboxyatractyloside (CATR), in the plants.

Consultation submissions

Seven submissions were received in response to this proposal.

Two submissions from professional organisations (e.g. representing clinical practitioners and pharmacists) fully supported the proposed changes. In contrast, five responses from industry representatives opposed removing the ingredients from the Determination entirely, and proposed alternative changes to mitigate risk. A range of feedback and concerns were provided in the consultation responses. The main points are discussed below.

TGA response

The TGA thanks stakeholders for their submissions.

Removal not in line with international regulation

Some respondents noted that other overseas regulators permit the use of *Xanthium* spp. in therapeutic products, and that removal of this ingredient would not be consistent with comparable overseas regulation. Examples of jurisdictions that use less restrictive safety requirements for *Xanthium* spp. were provided; Health Canada, Korea, Hong Kong SAR, Japan, Singapore, and China (via the Pharmacopoeia of the People's Republic of China [PPRC]). However, specific restrictions of Xanthium species and *Fructus Xanthii* imposed by other international regulatory bodies, other than Health Canada and China, have not been substantiated by respondents.

One respondent raised that the Norwegian Medical Products Agency, with some exceptions, does not permit importation of any medicinal products for personal use, to manage importation of illicit and counterfeit therapeutic goods. As discussed in the consultation document, the TGA is aware of the intention of the Norwegian Medical Products Agency to prevent personal import of medicinal products, however, *Xanthium strumarium* is expressly included in a list of herbs banned from import due to fitting the criteria of being 'poisonous herbs, herbs containing narcotic substances or herbs with strong effects or health risks', which are independently not permitted for import by private individuals[8].

Safety of processed *Xanthium* spp., tradition of use and regulatory impact on existing listed medicines

Many respondents noted that most adverse effects are primarily due to unprocessed plant material and/or remarkably high doses, that are not reflective of the listed medicine framework in Australia, where medicines on the ARTG are manufactured under stringent Good Manufacturing Practice (GMP) requirements. As there are currently no specific requirements for Xanthium ingredients in the Determination, and no current monograph for *Xanthium* spp. in the default standards, there is a plausible risk that medicines containing *Xanthium* spp. may not adhere to *materia medica* preparations. This has ramifications on potential catastrophic adverse events such as fatalities if legislative changes are not implemented for *Xanthium* spp.

Additionally, respondents raised the point that *Xanthium* spp. have been used in TCM formulations for thousands of years and have been available for use in listed medicines in Australia since at least 2007, mostly without any described cases of adverse events. They also emphasised that *Xanthium* spp. are considered important ingredients in TCM for the treatment for chronic rhinitis and sinusitis, and that safety mechanisms can be built within the listed medicine framework to ensure that the ingredient is safe for self-selection by Australian consumers. One respondent also flagged that there are currently no well-established or authoritative substitutes for *Xanthium* spp., although no further information was provided for consideration.

A number of respondents raised concerns that *Xanthium* spp. are often included in complex herbal formulations, and that removal of *Xanthium* spp. from the Determination would have a large regulatory impact on the industry. Respondents argued that medicine sponsors have invested in research and development of their products, and since the ingredients work synergistically within the formulation, this may affect the efficacy and value of the products. Further to this, sponsors often hold safety and efficacy evidence based on the whole formulation rather than individual ingredients, and removal of *Xanthium* spp. from the Determination and the formulations would therefore undermine the validity of that evidence.

In recognition of the safety of processed *Xanthium* spp., the apparent absence of adverse events associated with the appropriately-processed fruit, and the benefits of its long traditional use in TCM formulations, the TGA agrees to not remove *Xanthium* spp. from the Determination. However, the TGA notes the inherent toxicity of the ingredient in its unprocessed form due to the presence of CATR and ATR. To ensure the ingredient is safe and made available in low-risk medicines, risk mitigation in the form of restrictions is prudent, as proposed by most respondents.

Route of administration

The TGA has elected to restrict the route of administration for listed medicines containing *Xanthium* spp. to be for oral use only because available evidence does not support a history of safe use via other routes of administration. All current listed medicines that use these ingredients have an oral roue of administration, and hence this restriction will not affect the medicines currently on the market in Australia. This is also in line with the restrictions imposed on *Fructus Xanthii* by Health Canada.

Restriction on plant part

Some respondents suggested limiting availability of the plant to the medicinal part of the plant, known as the fruit or bur, to avoid usage of young plants that contain the toxic components in the leaves. Additionally, one respondent proposed addition of 'bur' to the plant part in the Code Tables.

The TGA recognises that the suggestion to add ‘bur’ to the plant part code tables aims to reduce ambiguity in identifying the correct part of the plant, which is colloquially known as a fruit but botanically classified as a bur composed of seed, fruit and bract tissue[9]. However, as per the TGA approved terminology for therapeutic goods, ‘Fruit includes the seeds, all the surrounding tissue layers, any persistent bracts and the individual fruit stalk, and may include any branching fruit stalks’, and thus ‘fruit’ is an appropriate description for the purpose of using the most correct plant part name. The TGA agrees that limiting the availability of *Xanthium* spp. to only the fruit reduces risk of this ingredient, as the young leaves of the plant are known to be toxic due to high concentrations of CATR[10,11,12,13]. Furthermore, the TGA is not aware of evidence indicating that other parts of the plant have a history of safe use or have been traditionally used medicinally. The availability of plant part will be limited to ‘fruit’, which is in alignment with restrictions imposed by Health Canada on *Fructus Xanthii,* the PPRC monograph for *Xanthii Fructus*[14,15] and recommendations made to the TGA by the Complementary Medicines Evaluation Committee at their 67th meeting in 2008 (CMEC 67).

Restriction on plant preparation and processing methods

All respondents who disagreed with removal of *Xanthium* spp. from the Determination proposed restricting the ingredient to specific preparation methods. These respondents agreed that heat

treatment significantly reduced the concentrations of the toxic components, in agreement with the methods of processing outlined in PPRC 2015[14] and 2020[15]. Indeed, some respondents suggested restricting to PPRC methods, while others only suggested 'heat processing and removal of spiny burs'. Some respondents added that these preparation methods align with PPRC, traditional *Materia Medica* and current restrictions from Health Canada.

The TGA agrees that processing according to the PPRC monograph substantially reduces CATR content and associated toxicity of the burs (fruits), as has been demonstrated by quantitative analysis methods[16,17]. According to PPRC 2020, these preparation methods involve drying the ripe autumnal fruits, stir-baking (application of dry heat, described in PPRC 2020 as: 'Place clean crude drugs in a pot, stir-bake on a gentle fire to the required condition, remove the drugs, and allow to cool') until the fruits are yellowish-brown, removing the spines and finally sifting. These methods are unchanged between PPRC 2015 and 2020.

Limiting *Xanthium* spp. in listed medicines to the form processed by stir-frying is in line with recommendations made by CMEC, and are consistent with international regulation of these ingredients, for example by Health Canada. Hence, the plant preparation for these ingredients is limited to 'cooked', the code table definition of which is: 'Herbal material that has been prepared in a traditional manner with the use of heat. Acceptable methods are roasting, baking, boiling, steaming and frying.' Here, the traditional manner means the stir-bake method defined by PPRC 2015 and 2020. To bring restrictions in line with traditional methods detailed in PPRC, we have added 'The plant part must be limited to fruit that is dried, cooked and had the spines removed' to clarify that the fruits must be processed by traditional methods, including removal of the spines.

The TGA will also restrict plant preparation to be dry, powder, and extraction preparations with water as the only solvent, to align with traditional extraction methods[15] and current literature[18,19,20]. This is also consistent with the majority of existing products containing *Xanthium* spp. on the ARTG, which have included extract dry concentrate, extract liquid concentrate and powder as plant preparation, and water as the extraction solvent.

CATR and ATR mandatory components with upper limit restriction

While some respondents support restriction of the toxic components of *Xanthium* spp., namely CATR, others support CATR be made mandatory component of these ingredients with a limit of 0.35%, to be consistent with the PPRC 2015 restriction. Another respondent disagreed that CATR and ATR should be assayed as mandatory components, stating that they have 'received information' that the Chinese Pharmacopoeial Committee regarded it unnecessary to limit CATR and ATR in PPRC 2020 following large-scale analysis of assay data suggesting that these components are largely eliminated after proper preparation and processing. However, respondents have not provided information to justify this.

The TGA was unable to access the rationale or supporting data used by the Chinese Pharmacopoeial Committee for removing the requirements in PPRC 2020 limiting CATR and ATR in processed *Xanthium* spp. burs used medicinally, as the rationale for these changes were not included in the 2020 version of the pharmacopoeia. The TGA notes that PPRC 2020 is not a default standard, and as such the preparation specifications detailed in PPRC 2015 are used alongside CMEC recommendations as supporting data when evaluating methods for improving safety of products containing *Xanthium* spp.

Contrary to the assertion that most products fall within the PPRC 2015 limits for CATR and ATR, published studies[16,17] indicate that commercially available non-Australian products reportedly containing roasted *Xanthium* spp. did not conform to limits specified in PPRC 2015 (not more than 0.35% CATR; not less than 0.10% and not more than 0.30% ATR). Jiang et al (2018) tested 18 samples of purportedly processed *Xanthium* spp. purchased either from pharmacies or local Chinese herbal medicine market demonstrated that 4 of 18 products contained higher ATR than permitted by PPRC 2015, and two contained levels of CATR close to the specified limit. Similarly, Nikles et al. (2015) tested 12 trade/import samples labelled as roasted, and found that 1 was above and 2 were at the 0.35% limit for CATR, while 1 was above 0.30% ATR and 4 contained below 0.10%.

These studies indicate that products available to consumers are not always compliant with PPRC monograph specifications for CATR and ATR content, despite being labelled as roasted/processed.

These components also vary depending on harvesting season of *Xanthium* spp.[19] as with other herbal ingredients. Therefore, maintaining upper limits on CATR and ATR as mandatory components of *Xanthium* spp. will significantly improve consistency and safety of products that use these ingredients, as is appropriate for low-risk listed medicines.

Maximum daily dose restriction

Many respondents suggested restricting the maximum daily dose of *Xanthium* spp. to 10 grams, in alignment with the PPRC (2015, 2020), traditional *Materia Medica*. This is similar to the maximum daily dosage recommended by CMEC 67 (9 grams per day), who referred to the maximum dosage specified in the PPRC 2005 available at the time.

The TGA agrees that a restriction on maximum recommended daily dosage will reduce the risks of using products containing *Xanthium* spp. This restriction will align with the maximum dosage as per PPRC 2020 of 10 grams per day. The TGA also notes that all but one product on the ARTG currently provides 10 grams/day or less of *X. sibiricum* or *X. strumarium*.

Maximum duration of use of 4 weeks

One respondent suggested restricting the duration of use to four weeks, to mitigate concerns associated with long term use, specifically the risk of toxic compounds accumulating in the body over time.

The TGA notes that there are a number of products currently listed in the ARTG that contain *Xanthium* spp. and have indications for conditions such as chronic rhinitis, which likely indicates prolonged use of the product. Considering the lack of adverse events associated with medicinal products containing *Xanthium spp.* in Australia, the current usage pattern of these ingredients may not result in significant risk. However, there is a lack of consistent evidence indicating long-term safety of using these ingredients, and a specific lack of clinical evidence for chronic use. As discussed in the consultation document, there is evidence from animal studies that the toxic compounds may accumulate in the body and cause accumulated harm over time[18,16] although this appears to be at least partially ameliorated by the heat treatment during processing. Furthermore, pharmacokinetic evidence in rats suggests that the toxic compounds are eliminated in under 24h, and hence are not likely to rapidly accumulate in the body if used at recommended doses[20]. Given the history of safe use and the pharmacokinetic profiles, the TGA considers that a restriction on duration of use is not necessary at this time.

Use in vulnerable populations

One respondent suggested addition of a pregnancy warning statement to medicines that contain *Xanthium* spp. to mitigate the risk of *in vivo* genotoxicity. The respondent suggested the phrase: 'Do not use if pregnant or likely to become pregnant, or during lactation.' The TGA notes that the adverse findings as per the reproductive toxicology study in zebrafish embryos by Chen et al. (2014)[21] as cited in Fan et al. (2019)[22] was conducted using aqueous extracts of *X. strumarium*, though it is unclear whether these are from fruit as processed in accordance with the PPRC 2015 and 2020.

The TGA acknowledges that there is a lack of robust data that demonstrates that these ingredients, when properly prepared, cause toxicity to unborn babies or newborns when used by a pregnant or lactating caregiver. Further, there is no clinical data to demonstrate safety under these conditions, as well as in children and adolescents. As such, the TGA elects to implement a restriction to contraindicate the use of *Xanthium* spp. in those who are lactating, pregnant, intending to get pregnant and in children. This only affects any products directing use specifically to these population groups.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA has decided not to remove *Xanthium* spp. from the Determination. Going forward, sponsors will need to declare the mandatory components in the medicine, limit recommended

maximum daily dose, restrict the plant part and preparations, and ensure products are not directed for use in children and those who are likely to become pregnant, pregnant, and lactating.

Affected ingredients

- XANTHIUM SIBIRICUM
- XANTHIUM STRUMARIUM

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	Proposed specific requirements
XANTHIUM SIBIRICUM	-	The requirements specified in paragraphs (a) to (h) below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. (a) Carboxyatractyloside and atractyloside are mandatory components of Xanthium sibiricum. (b) The concentration of carboxyatractyloside must not be more than 0.35% of Xanthium sibiricum. (c) The concentration of atractyloside must not be more than 0.3% of Xanthium sibiricum. (d) The route of administration for medicines that contain Xanthium sibiricum must be limited to oral. (e) The plant part must be limited to fruit that is dried, cooked and had the spines removed. (f) The plant preparation must be limited to dry, powder, and extraction preparations with water as the only solvent. (g) The maximum recommended daily dose of the medicine must not provide more than 10 g of Xanthium sibiricum. (h) The medicine must not be directed for use in children, those who are pregnant, likely to become pregnant, or lactating.

Ingredient name	Existing specific requirements	Proposed specific requirements
XANTHIUM STRUMARIUM	-	The requirements specified in paragraphs (a) to (h) below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. (a) Carboxyatractyloside and atractyloside are mandatory components of Xanthium strumarium. (b) The concentration of carboxyatractyloside must not be more than 0.35% of Xanthium strumarium. (c) The concentration of atractyloside must not be more than 0.3% of Xanthium strumarium. (d) The route of administration for medicines that contain Xanthium strumarium must be limited to oral. (e) The plant part must be limited to fruit that is dried, cooked and had the spines removed. (f) The plant preparation must be limited to dry, powder, and extraction preparations with water as the only solvent. (g) The maximum recommended daily dose of the medicine must not provide more than 10 g of Xanthium strumarium. (h) The medicine must not be directed for use in children, those who are pregnant, likely to become pregnant, or lactating.

References – Xanthium species and risk of toxicity

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4. Phenoxyethanol

Background

The consultation document proposed to reduce the maximum permitted concentration of 2-Phenoxyethanol (phenoxyethanol) to 1% in topical listed medicines for dermal application. This change aims to align with levels specified in Schedule 6 of the Poisons Standard for cosmetic preparations and international regulatory limits. Additionally, it proposed amending the restrictions to exclude the use of medicines intended for use in the eye.

Consultation submissions

Six submissions were received in response to this proposal.

All six submissions, including those from industry representatives and organisations and colleges representing health professionals, fully endorsed the proposal to reduce the maximum permitted concentration of phenoxyethanol in topical medicines for dermal application from 15% to 1%. However, two submissions raised concerns about the proposed restriction in relation to “not to be included in medicines intended for use in the eye”.

TGA response

The TGA thanks stakeholders for their submissions.

The proposed restriction on excluding phenoxyethanol from medicines intended for use in the eye is based on evidence showing that phenoxyethanol can cause ocular irritation.[23] The intent of these restrictions is to emphasise the need to avoid contact with the eye due to this irritation risk, rather than to regulate topical eye medications, which are registered medicines and not listed medicines.

One industry representative raised concern that the current entry already states, “only for use in topical medicines for dermal application” and that adding restrictions related to the eye seems redundant and potentially confusing. However, since topical medicines for dermal application can be used on the face, there is a high probability that the medicine could inadvertently come into contact with the eye. Therefore, the proposed restrictions are meant to underscore the importance of avoiding eye contact.

Another industry representative recommended that the TGA may wish to consider adding ingredients that are in the Poisons Standard for cosmetic use to the Determination, with a specific requirement that they are only for use in topical medicines for dermal application. They reasoned that these ingredients have been included in the Poisons Standard through public consultation, consideration by Advisory Committees on Chemicals and/or Medicines Scheduling and decisions made by a Delegate of the Minister for Health. The TGA thanks industry for bringing this to our attention. However, the proposed change with respect to phenoxyethanol was initiated due to safety concerns related to use of phenoxyethanol at a concentration up to 15% (i.e. above the intended concentration of 1%). Additionally, any such changes fall outside of the scope of this consultation.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA will implement new requirements to reduce the maximum permitted concentration of phenoxyethanol in topical medicines for dermal application from 15% to 1%, as presented for consultation. Additionally, there will be minor formatting changes for the purpose of improving the internal consistency of the Determination.

Affected ingredient

- PHENOXYETHANOL

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	Proposed specific requirements
PHENOXYETHANOL	Only for use in topical medicines for dermal application. The concentration of phenoxyethanol in the preparation must not exceed 15%.	The requirements specified in paragraphs (a) to (b) below apply to a medicine that contains the ingredient that is: - listed in the Register before 1 March 2025; and - released for supply before 1 March 2026. (a) Only for use in topical medicines for dermal application. (b) The concentration of phenoxyethanol in the preparation must not exceed 15%. The requirements specified in paragraphs (c) to (d) below apply to a medicine that contains the ingredient that is: - listed in the Register on or after 1 March 2025; or - released for supply on or after 1 March 2026. (c) Only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye. (d) The concentration of phenoxyethanol in the preparation must not exceed 1%.

References - Phenoxyethanol

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5. Clarification of hydration state for Rutoside

Background

The consultation document proposed changing 'rutoside (rutin)' to 'rutoside trihydrate' to align with the original evaluation by the Complementary Medicines Evaluation Committee (CMEC).[24] It seems there is a discrepancy between what was considered by CMEC and what is currently on the Determination.

Consultation submissions

Four submissions were received in response to this proposal.

Two submissions fully supported the proposed ingredient name change. The other two respondents, while not opposing the change, raised concerns about potential unintended consequences that extend beyond labelling changes. These concerns may necessitate additional flexibility regarding transitional arrangements. Additionally, questions were raised about the lack of a compositional guideline or default standard, apart from the CMEC assessment, that specifies that rutoside should be rutoside trihydrate, and thus expected to comply with the British Pharmacopoeia monograph. Furthermore, the hydration state in the ARTG may be relevant for labelling of a medicine, it does not appear to provide any added value to consumers.

TGA response

The TGA thanks stakeholders for their submissions.

CMEC assessment

Stakeholders raised questions about the lack of a compositional guideline or default standard apart from the CMEC assessment that specified that rutoside should be rutoside trihydrate. As outlined in the consultation paper, the CMEC considered a TGA evaluation of the trihydrate form of rutoside. Further that a monograph exists in the British Pharmacopoeia, that sponsors are required to comply with. As such this proposal is to remove the discrepancy between what was considered at CMEC 45 and what is on the current Determination, rather than imposing additional regulatory requirements.

Unintended impacts

The TGA is aware that there may be unintended consequences as a result of changing "rutoside" to "rutoside trihydrate", which was also mentioned in the submissions received. As such, the TGA is seeking this information from sponsors and will make necessary arrangements to ensure minimal regulatory impact for existing sponsors.

Hydration states

One stakeholder stated that the hydration state may be relevant on the label but of little value to consumers and could be overwhelming. However, it is a requirement of the Therapeutic Goods Order No. 92 – Standard for labels of non-prescription medicines that the full name of the active ingredients, including its hydration state, must clearly be stated on the labels. This ensures that consumers and healthcare professionals have precise information about the product's composition.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. Sponsors of affected medicines will be informed of the proposal to vary their ARTG entry under subsection 9D(1) of the *Therapeutic Goods Act 1989*, and arrangements will be made for consent to supply therapeutic goods that do not conform with paragraphs 8(1)(b) and 9(1)(b) of the Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines commencing 1 March 2025 for a specified period.

Affected ingredient

- RUTOSIDE

Final changes to specific ingredient requirements in the Determination

Ingredient name	New Ingredient name
RUTOSIDE	RUTOSIDE TRIHYDRATE

References - Rutoside

[24] Complementary Medicines Evaluation Committee (CMEC) Extracted Ratified Minutes, Forty-fifth Meeting, 23 April 2004: https://www.tga.gov.au/sites/default/files/cmec-minutes-45.pdf.

Timetable

The confirmed changes to the Determination will commence on **Saturday 1 March 2025**.

The transition period of 1 year will end on **Sunday 1 March 2026** unless otherwise specified.

Enquiries

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

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary Medicines Evaluation Section	2 December 2024

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