Australian Government
Department of Health
Therapeutic Goods Administration

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

Final Decisions

Version 1.0, December 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 changes to ingredient requirements in the Determination were presented for consultation after they were reviewed and categorised as being of low-negligible risk. The purpose of this consultation was to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes prior to their implementation.

This document outlines the final decisions made regarding the proposed changes to ingredient requirements specified in the Determination, in consideration of the consultation submissions received. These changes will commence on **1 March 2023** (see schedule for low-negligible risk changes for 2022-2023). Following commencement of the updated Determination, sponsors will be provided with a 12-month transition period to align their products with these changes.

Public consultation

The consultation opened on **4 August 2022** and closed on **15 September 2022**.

The TGA thanks all respondents for their participation in this consultation process. A total of 9 responses to the consultation were received from professional bodies, industry organisations, and medicine sponsors/brands and manufacturers.

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 Submissions received with claims of confidentiality or privacy have been redacted or remain unpublished as specified by the submitter.

Transition expectations

All changes proposed as a result of this consultation will commence on**1 March 2023**, and will include a 12-month transition period until **1 March 2024**.

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

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

Proposed changes to requirements for listed medicine ingredients

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

Background

The TGA proposed to update the specific requirements of *Chelidonium majus* and *Larrea tridentata* to clarify the warning statement required for these ingredients, and remove the required statement to only use the ingredient under the supervision of a healthcare professional. The advice to use under medical supervision 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. Further details regarding the background of this issue and the proposed changes are included in the Consultation Document provided on the Consultation Hub.

Consultation submissions

Many respondents agreed with the need to promote consumer safety. A range of feedback and concerns were provided in the consultation responses. The main concerns are discussed below.

Length and complexity of warning statement

Some respondents raised that the length and complexity of warning statements is likely to be an impediment to consumer understanding, and appropriate action. There is also limited availability on labels for long warning statements. These respondents proposed that the warning statement should be succinct while retaining the meaning and intent for consumers.

Referral to a nurse practitioner

One respondent supported the changes and suggested the warning statement should also refer to nurse practitioners in addition to doctors to diagnose liver harm and refer appropriately.

Reference to non-specific symptoms of liver injury

Some respondents suggested the inclusion of general symptoms in the warning (nausea, vomiting, abdominal pain, loss of appetite, tiredness and weakness) could cause confusion or alarm because the symptoms can apply to other conditions not just liver injury. Further, *Chelidonium majus* is used for Irritable Bowel Syndrome (IBS) relief and for digestive discomfort so reference to general digestive symptoms can cause confusion. Respondents suggested that warning statements for liver injury do not need to be the same for all products and rather can be tailored to each individual ingredient and the risk of liver injury.

Use of the term 'Warning'

Some respondents questioned when the term 'WARNING' needs to be included. A respondent raised that having multiple warning statements on a label each with the term 'WARNING' encroaches space on the label. It may be sufficient to include the word 'WARNING' once, and include all warning statements under the one heading. Some respondents suggested to only include 'WARNING' using a risk-based approach and using it for very high-risk warning statements. One respondent suggested the low-risk of liver injury associated with *Chelidonium majus* and *Larrea tridentata* may not warrant the inclusion of the term for these ingredients.

Alternative warning statements proposed

Some respondents proposed a range of alternative warning statements that addressed concerns discussed above. Some statements only included symptoms of serious or late stage liver injury (yellowing of skin or eyes, dark urine), while others only referred to the risk of liver harm and advised consumers to see a doctor if symptoms develop or worsen. Another proposed statement suggested a shorter wording to maintain the same intent and meaning as proposed by the TGA.

Replacement of common names of the ingredients

Respondents did not oppose replacement of the common names of the ingredients (Greater celandine and Chaparral) as proposed in the consultation document.

TGA response

Length and complexity of warning statement

The TGA supports shorter, more effective statements that best achieves consumer safety and acknowledges suggestions from respondents to reduce the length of the warning statement. The warning statement has been revised below to communicate the same intent more concisely, including removal of the words 'in some people', amendment of 'stop using this product' to 'stop use', amendment of 'experience yellowing of the skin/eyes' to 'have yellowing skin/eyes', 'loss of appetite' to 'appetite loss', remove 'vomiting' as it would normally be preceded by nausea, and replacement of 'unusual tiredness, weakness' with 'unusual fatigue'. Further wording reductions are also described below.

Referral to a nurse practitioner

The TGA notes other healthcare professionals such as nurse practitioners may play a role in diagnosing, assessing, or treating patients who may not have access to a regular doctor. Due to the seriousness of liver injury, accurate and prompt investigation and diagnostic testing is required which needs input from a medical doctor in most circumstances. Noting respondents sought the shortest wording possible for a warning statement, the warning statement will maintain to 'see a doctor' rather than referring to various types of healthcare professionals. Although other wording such as 'seek medical assistance', 'see/contact a medical professional', may be broader, this wording is longer and ultimately achieves the same outcome as 'see a doctor' because other professionals will most likely need to refer patients for review and treatment by a doctor. This would cause unnecessary delays in early diagnosis. It is expected that in the unlikely circumstance that consumers do not have access to a doctor, that they would seek access to the most appropriate available medical professional for assistance.

Reference to non-specific symptoms of liver injury

Liver injury from *Chelidonium majus* and *Larrea tridentata* typically presents as hepatocellular and clinically present similar to acute viral hepatitis (LiverTox, 2022a) (LiverTox, 2022). Initial symptoms for this type of liver injury are 'an insidious onset of fatigue and nausea, followed by anorexia, abdominal discomfort (liver discomfort) and then dark urine and jaundice' (LiverTox, 2019d).

Although the risk of liver injury is a rare event, it can arise from normal use in accordance with usage instructions for these medicines. As such the proposed warning requires greater information rather than references to just having an existing liver problem which was suggested for the wording of the warning by some respondents. This is to enable consumers to know when to cease the product and seek medical attention.

Early signs and symptoms are important so that consumers can take preventative action before late-stage liver injury occurs. It is not appropriate to only list symptoms of liver injury such as jaundice/yellowing of the eyes or skin or dark urine which are symptomatic of late-stage liver injury such as acute liver failure (LiverTox, 2019a). One respondent provided an example of a prescription medication (flucloxacillin), that contains a condensed liver warning without reference to detailed symptoms, however these medications are prescribed by medical professionals, and used under medical supervision. Conversely, listed medicines are available for self-selection and administration and patients can access these medications without medical advice and supervision.

In order to balance the need of raising consumer awareness of the symptoms of early-stage liver injury but also contrast such general symptoms (such as common digestive symptoms) the proposed warning statement has been revised to refer to 'unusual' fatigue, nausea, appetite loss, abdominal pain or dark urine. This allows consumers to observe and assess whether their symptoms are unusual, differ from any regularly experienced abdominal discomfort, and if symptoms are concerning seek medical help accordingly.

Use of the term 'Warning'

The term 'WARNING' has been removed in the warning statement noting the rare/uncommon risk of liver injury associated with *Chelidonium majus* and *Larrea tridentata* (LiverTox, 2022) (LiverTox, 2022a). Accordingly the statement has also been clarified to state the risk is rare, and combined with the words 'may' harm the liver, clarifies overall that the risk of the adverse event is unlikely. This has also replaced the previously proposed words 'in some people' which was less informative. With the inclusion of this warning statement, these ingredients are considered to be suitable for use in low-risk medicines. This wording achieves a shorter and informative warning statement. The term 'WARNING' has been reserved for strong associations and higher risk situations.

Replacement of common names of the ingredients

The common names of the ingredients (Greater celandine and Chaparral) have been replaced with the ingredient names specified in the Permissible Ingredients Determination: *Chelidonium majus* and *Larrea tridentata*.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. The following two ingredients will be amended within the Permissible Ingredients Determination commencing on 1 March 2023 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

Affected ingredients

- CHELIDONIUM MAJUS
- LARREA TRIDENTATA

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New 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'.~~ 'In rare cases, *Chelidonium majus* may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain or dark urine.'
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'.~~ 'In rare cases, *Larrea tridentata* may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain or dark urine.'

2. Liver injury associated with *Valeriana officinalis*

Background

The TGA proposed specific requirements for the inclusion of a warning statement to address the risk of liver injury associated with products containing *Valeriana officinalis* ('valerian'). The proposed warning statement was intended to communicate the potential for liver injury and to reduce the risk of serious liver damage by recommending cessation of the product and consultation with a doctor if symptoms of liver injury are experienced. Further details regarding the background of this issue and the proposed changes are included in the Consultation Document provided on the Consultation Hub.

Consultation submissions

There were nine responses to this consultation. Two respondents agreed with the need to promote consumer safety, however suggested alternative wording. One respondent did not support the proposal but proposed rewording of the warning statement as a risk mitigation step. Six respondents from the complementary medicines industry disagreed with the need to include the warning statement. A range of feedback and concerns were provided in the consultation responses. The main concerns are discussed below.

Dose and quality of valerian preparations

One respondent raised concern that the proposed warning statement does not consider any dosages, and therefore would be applicable to low-dose products, noting some manufacturers produce low dose valerian products (equivalent to ~57 mg dry herb per day), compared to an equivalent dry herb daily dose of valerian which is 900mg to 9g per day in herbal tea. Another respondent suggested that rather than inclusion of a warning statement, valerian products should be limited to a maximum daily dosage of 1000mg of raw herb.

The quality of valerian preparations and potential for contamination was also raised as something to be considered when assessing adverse events related to valerian products. Responses suggested there may be a correlation between poor quality products and liver-related adverse events. Issues were suggested such as high amounts of solvents from liquid mixtures used in manufacturing tablets/powders, impurities such as pyrrolizidine alkaloids which can cause liver injury, and some overseas products that may not have strict quality controls for medicines and herbal food products.

International regulation

Several respondents were concerned that the proposed warning statement is inconsistent with international monographs and reports on valerian. Specifically monographs from the EMA, Health Canada, and Germany do not report that liver injury is associated with valerian use.

The WHO monograph on selected medicinal plants, Natural Medicines Database, the National Toxicology Program from the US Department of Health and Human Services, and the NIH LiverTox database all have reports of liver injury caused by valerian. However, respondents raised concerns that the reports did not establish a clear causal link between the herb and liver injury as the case reports include individuals using concomitant medications or combination

herbal products, did not assess product quality, or lacked standardised causality assessments such as Roussel Uclaf Causality Method (RUCAM).

Causality of liver injury

Several respondents stated there is a lack of a causal relationship between liver injury and valerian intake suggesting that causality for herb induced liver injury (HILI) requires a thorough assessment, e.g. using RUCAM or WHO Causality Assessment, and the most thorough assessment is considered to be a RUCAM analysis.

One respondent stated that the published literature case reports of liver injury associated with valerian did not present sufficient information to establish causality using a RUCAM analysis. In the two instances where a RUCAM analysis was performed, the respondent contended that it was incorrect in one case (KOENIG, et al., 2021), while in the other case information was not available to verify (GARCIA-CORTES, et al., 2008). It was further noted that some case reports of liver injury involve food supplements and teas which may not be manufactured to the same standard as medicines and may have had contamination with toxins such as pyrrolizidine alkaloids or heavy metals that may have contributed to liver injury.

Additional publications cited

Several respondents cited other literature reviews and systematic reviews involving valerian use to demonstrate that valerian does not cause liver-related adverse events.

One systematic review and meta-analysis of 60 studies (total subjects n=6,894), was cited to evaluate the effectiveness of valerian as a sleep aid and liver related adverse events were not reported in this study (SHINJYO, et al., 2020). A second systematic review for valerian was an analysis of 37 studies: 29 controlled trials of efficacy and safety of valerian, and 8 open label trials for safety only (TAIBI, et al., 2007).

One respondent provided a literature search of 13 studies of valerian use published since the completion of the EMA HMPC assessment report in 2016; the respondent claimed these studies did not contain any evidence of liver injury related to valerian use. The 13 studies cited includes a total study population of n=429. Another respondents provided a literature search of 11 studies published since completion of the EMA HMPC assessment report in 2016 that also claimed the studies did not contain evidence of liver injury related to valerian use.

One respondent suggested the evidence for liver injury is not substantial or conclusive to warrant a label warning without expert scientific assessment, considering the widespread global use of valerian. The respondent stated over 800,000 adults in the United States (US) reported use of valerian in the previous 30 days in 2012 (CLARKE, et al., 2015).

Incidence of liver injury

Several product sponsors raised that they did not have reports or had very few reports of adverse events relating to liver injury for their own products that contain valerian.

One sponsor advised that for each of the adverse events reported for their product, a RUCAM assessment was not possible, but a WHO assessment established a possible causal link between valerian and liver injury for five of six cases. The sponsor advised that concomitant drugs were

used in all cases, so it was not possible to determine whether there was a causal relationship between their valerian product and liver injury.

One respondent noted that the worldwide WHO VigiAccess database has only reported 3% of all side effects (n=919) associated with valerian to hepatobiliary disorders, with a lack of further details to establish whether concomitant ingredients may have contributed to liver injury. Another respondent stated there were 75 adverse events relating to hepatobiliary disorders and investigations out of 915 case reports for valerian (equating to 8% of all adverse event report cases). This respondent also noted that in the VigiAccess database there are 3672 out of 193248 case reports (equating to 1.9% of all cases) of liver related adverse events for acetylsalicylic acid (aspirin) which may illustrate the general reporting pattern could be 'basic noise' of specific symptoms that lack verified, comprehensive and causality assessment of case records.

Some respondents also noted their concern that when looking into single case reports in the TGA Database of Adverse Event Notifications (DAEN), during a period of 51 years, only 16 liver-specific adverse event cases were reported for valerian with only three liver related adverse events which were attributed to valerian as the sole active ingredient.

Overall, all but one respondent from the complementary medicines industry did not consider that the incidence of adverse events warrants a safety signal requiring a warning statement for valerian. One respondent suggested if a warning statement were to proceed, then the extremely rare nature of liver injury should be reflected in the warning to provide a balanced comparison to existing products with minimal or no warnings.

Comparison to other products that may harm the liver

Two respondents stated that other self-selected products such as paracetamol, aspirin, and food such as alcohol and sugar can harm the liver yet these products do not require a label warning for liver injury. One respondent called for a whole-of-government review of self-selected products (such as food) so that warnings and their effectiveness for consumers can be considered collectively. The respondent also compared the proposed warning statement with existing listed medicine ingredients where some have shorter warning statements for liver injury.

Warning statement – length, content, and inclusion of the term 'WARNING'

Similar to concerns raised for *Chelidonium majus* and *Larrea tridentata*, some respondents stated that the proposed warning statement is too long and encroaches on the label space available for products. Some respondents were concerned that the length and complexity of the warning statement may be an impediment to consumer understanding and appropriate action.

Similar to the concern raised for *Chelidonium majus* and *Larrea tridentata*, one respondent supported the changes and suggested the warning statement should also refer to nurse practitioners in addition to doctors to diagnose liver harm and refer appropriately.

One respondent suggested the proposed warning statement Valerian may harm the liver 'in some people' is inaccurate because this suggests that liver injury is likely, that some consumers will experience liver harm or that it is predictable, common and expected and does not reflect the rarity or idiosyncratic nature of liver injury associated with valerian.

One respondent suggested the risk of liver injury for valerian may not warrant the use of the term 'WARNING' and the term should be reserved for ingredients with very high-risk to ensure prominence. Another respondent suggested it is sufficient to only include the term 'WARNING' once when multiple warning statements are required and grouped together.

Reference to non-specific symptoms of liver injury

One respondent raised that valerian is indicated as a sleep aid and the symptoms of tiredness and weakness described in the proposed warning statement are expected effects of taking valerian. 'Unusual fatigue' was suggested as a less confusing symptom. Further, the respondent suggested non-specific gastrointestinal symptoms are common and can be caused by a range of other conditions. This may cause confusion to consumers if these symptoms are present in a warning statement if valerian is not the cause of the issue. The respondent suggested this may cause delay of diagnosis of other conditions or the real cause of the liver issue.

Alternative warning statements proposed

Two respondents did not dispute the need for a warning statement, however, many of the respondents including those that did not support a warning statement, suggested a range of amendments to the proposed wording to address the concerns discussed above.

The warning statements proposed included stating that the incidence of liver injury is very rare and not clearly established, or is only suspected. Similar to the statements proposed for *Chelidonium majus* and *Larrea tridentata*, some proposed statements only included symptoms of serious or late-stage liver injury (yellowing of skin or eyes), while others only referred to not taking valerian if consumers had an existing liver problem, or stated valerian may harm the liver, and advised consumers to see a doctor of symptoms develop or worsen. Other suggested statements referred to 'unusual' digestive symptoms and fatigue to avoid consumer confusion between general digestive symptoms and tiredness and weakness.

Where alternate warning statements were provided, respondents did not oppose inclusion of the common name 'valerian' as proposed in the consultation.

TGA response

The TGA acknowledges there is concern from the complementary medicines industry regarding the proposed warning statement for liver injury associated with valerian. As noted in the consultation document, the TGA understands the nature of valerian associated liver injury is idiosyncratic. Idiosyncratic drug induced liver injury (DILI) is largely independent of the dose and duration of the medication (FONTANA, et al., 2022). Further the lack of knowledge and awareness of potential Herb Induced Liver Injury (HILI) from widely used supplements may result in a failure to identify a causal association which can lead to under-reporting. This causes considerable challenges when establishing a clear causal link between liver injury and a specific herbal ingredient. Such challenges can be overcome by increasing awareness of the risk of HILI among consumers and healthcare practitioners. The TGA acknowledges the concerns and the main issues raised are discussed below.

Dose and quality of valerian preparations

As noted in the Consultation Document, liver injury associated with valerian is idiosyncratic, and idiosyncratic HILI is not generally dose-dependent. The mechanism of action of liver injury for valerian is not known to be dose related. It is possible that modern, non-traditional manufacturing methods that concentrate certain components of the herb may change the way consumers react to these medicines. Based on the currently available evidence, a maximum daily dosage limit is not considered an appropriate risk mitigation strategy for idiosyncratic liver injury.

The TGA acknowledges that the quality of valerian products on the international market is highly diverse, and variable product quality may impact the incidence of adverse events. However, the TGA has received reports of serious liver injury for single ingredient valerian products included in the ARTG. Listed medicines in Australia must be manufactured under Good Manufacturing Practice and comply with other quality requirements such as the Therapeutic Goods Order No. 101 - Standard for tablets, capsules and pills. It is further noted that issues of quality contamination would be associated with a clear cluster of adverse events, which is not evident in the reports received by the TGA or internationally.

International regulation

The TGA acknowledges that overseas jurisdictions including the EMA, Germany, and Health Canada have not included a warning regarding liver injury for valerian products. The EMA HMPC assessment cites a 30 day toxicity study in rats of 600mg/kg of valerian root extract/day to demonstrate that the use of valerian can be considered to be safe and does not demonstrate adverse liver effects (EMA, 2016a). However, idiosyncratic liver injury is difficult to replicate in animal models (FONTANA, et al., 2022). It is further noted that the EMA HMPC Assessments were completed in 2016 and the German Commission Monograph was published in 1985. Both assessments are therefore dated, and there is emerging safety data which is more recent and has not been included in these reports. General warning statements to see a doctor if symptoms worsen during use of the product which are present in the Health Canada and EMA monograph do not effectively inform consumers about possible liver injury, nor direct cessation of use and therefore are not considered to be appropriate statements to mitigate the risk of adverse events. The TGA also notes that the current absence of a liver warning in other jurisdictions is not reasonable justification for avoiding regulatory action where currently emerging evidence indicates mitigation is warranted to reduce the risk of serious outcomes.

Causality of liver injury

Challenges and methods of establishing causality of HILI

The TGA acknowledges the challenges in establishing a diagnosis for idiosyncratic drug induced liver injury (DILI) or herb induced liver injury (HILI) because of the need to exclude more common competing causes of liver injury, variable drug latency, and variable clinical manifestation. Further challenges of establishing causality can stem from the lack of knowledge and awareness of potential liver injury from herbal supplements which may result in the causative agent (i.e. the herbal medicine) to go unrecognised by both patients and health care professionals (FONTANA, et al., 2022). Another critical challenge in pharmacovigilance is incomplete information for spontaneous reports of individual cases.

The TGA notes that several respondents cited the RUCAM causality assessment method as being reliable, standardised and evidence based. The TGA agrees that the RUCAM causality assessment method provides a standardised assessment for HILI. However, applying the RUCAM retrospectively often means some data is unavailable for analysis. Nevertheless it can be a useful tool where data allows, along with expert opinion. One respondent was concerned that drug re-challenge was missing information for several of the case reports in the consultation document. However, re-challenge is rarely undertaken in clinical practice and is best avoided due to ethical concerns given the potential for further injury, and to avoid a more severe and possibly fatal reaction (CHALASANI, et al., 2021).

Several practice guidelines written on idiosyncratic DILI or HILI state that structured expert opinion is frequently used in clinical research studies and is shown to be as useful as RUCAM (FONTANA, et al., 2022), (CHALASANI, et al., 2021) and (LiverTox, 2019). Expert opinion can also account for atypical cases, interrupted drug exposure and synthesis of subtle clues including liver histology in published literature (FONTANA, et al., 2022). Consensus expert opinion after a thorough evaluation for competing aetiologies is considered by some to be the current gold standard for establishing causality in individuals with suspected DILI (CHALASANI, et al., 2021).

Noting the challenges of establishing causality, the TGA has determined a causal link between valerian and liver injury using expert opinion, clinical assessment and RUCAM analysis.

TGA assessment of the causal relationship between valerian and HILI

One respondent raised concern with the case reports cited in the NIH LiverTox database, stating that the reports lacked standardised, systematic causality assessments such as a RUCAM or WHO assessment. As noted above, several practice guidelines on idiosyncratic DILI or HILI state that consensus expert opinion after a thorough evaluation is considered to be the gold standard for establishing causality. The NIH LiverTox database lists valerian as a probable rare cause of liver injury (LiverTox, 2020). It is noted that the LiverTox database content is subject to review by an External Expert Review committee comprised of three experts in DILI, hepatology, pharmacology and/or herbal supplement safety (LiverTox, 2022b).

The TGA notes there was sufficient data for RUCAM analysis in several case studies cited in the NIH LiverTox database entry for Valerian to support possible and probable causal relationships to the suspected medicines, including two cases with valerian reported as the single suspected ingredient (COHEN & TORO., 2008), and (VASSILIADIS, et al., 2009).

Another of the case reports cited in the NIH LiverTox database (GARCIA-CORTES, et al., 2008) was considered by one respondent to have insufficient information for a causal assessment. However, the TGA notes that the authors of this case study reported that all cases were evaluated by three independent experts using clinical judgement, as well as a RUCAM analysis. While the article did not include sufficient information to verify the reported RUCAM score, other details in the article indicated a comprehensive assessment was applied, with other causes excluded. The same respondent also reported insufficient data for analysis in another study (MACGREGOR, et al., 1989) that was also cited in the NIH LiverTox database. The TGA notes that serological tests to exclude other causes were reported by the authors, as was positive de-challenge, which supported the conclusions of the authors of the suspected causal role of Valerian-containing herbal medicines in these cases.

As such the case studies cited in the NIH LiverTox database have sufficient information for standardised causality assessment by expert review and/or RUCAM scoring to support the LiverTox likelihood score assigned to valerian of 'C: a probable rare cause of clinically apparent liver injury'.

A respondent raised concerns about another study cited in the TGA consultation document that the RUCAM analysis had been incorrectly applied (KOENIG, et al., 2021). While the TGA agrees that the RUCAM analysis appears to have been incorrectly calculated for certain aspects, a re-assessment by the TGA resulted in the same score of +6 (probable). It is however noted that this causality rating applied to the suspected medicine, which contained other herbal ingredients that have been associated with liver injury, therefore this case was not considered pivotal in TGA's review.

The TGA also assessed the causality of Australian adverse events in the DAEN using a combination of clinical expertise and RUCAM analysis, where data allowed, which confirmed a causal relationship between valerian and liver injury. Thus, the TGA confirmed that there is a causal relationship between valerian and liver injury using standardised assessment methods for both locally reported adverse events, and those in reported literature.

The TGA presented information regarding local and international adverse event reports to the Advisory Committee on Complimentary Medicines (ACCM) for further expert advice on the strength of the relationship between valerian and liver injury, whether risk mitigation is warranted and the potential effectiveness of risk mitigation measures such as a warning statement. ACCM recommended that there is an association between valerian use and liver injury which is very rare but can be severe, that risk mitigation is warranted and that mitigation strategies such as a label warning and broader education are appropriate.

Additional publications cited

Two respondents conducted independent literature reviews, and two other respondents cited systematic reviews for valerian products as evidence demonstrating that valerian use is safe, based on the lack of liver related adverse events reported.

The TGA notes that several studies in these literature reviews either did not collect or report adverse events and therefore cannot accurately demonstrate that liver-related adverse events would not occur. One respondent provided a literature review of 13 studies published since the completion of the EMA HMPC assessment report in 2016 that included a total study population across all 13 studies of n=429. Of these 13 studies, 6 either did not collect or did not report adverse events (n=204). Further in the remaining 7 studies (n=225), liver-related adverse events were not reported. Thus this literature review only demonstrated that liver-related adverse events did not occur across a small, combined study population of 225. Another literature review provided by a respondent comprised of 11 studies published since completion of the EMA HMPC assessment report in 2016. The respondent noted that adverse events were not reported in 4 studies, did not occur in 5 studies, or if adverse events were reported there was no difference between intervention and placebo. These publications were cited to demonstrate that the safety profile of valerian has not changed since the EMA assessment report. However the TGA notes that the provision of a selection of 11 studies or 13 studies does not provide an accurate representation of very rare adverse events, particularly where several studies did not report on adverse events. Without analysing study duration, population, dose

and valerian extract type, the provision of a selection of studies without any systematic review cannot support the safety profile to exclude the risk of liver injury of valerian with accuracy.

In one systematic review and meta-analysis cited where adverse events data was collected, but no liver-related adverse were reported, the number of subjects in the 60 studies was n= 6,894 (SHINJYO, et al., 2020). It is noted that this review included several valerian preparations including hydroalcoholic extracts, aqueous extracts, unknown extracts, whole root, isolates and herbal combination at various doses. The treatment duration for each individual study varied from single days to weeks, and each individual study had a range of study subjects (n=5 to n=2462). Given that this review, across all studies does not have a standard valerian extract type, standard doses, intervention duration and study population, it is not possible to establish that liver-related adverse events will not occur for valerian, noting the TGA has received reports of this.

The TGA notes that one systematic review cited by a respondent (TAIBI, et al., 2007) specifically states that 'caution should be exercised in the use of valerian by patients who have a history of liver disease, those at risk of liver dysfunction, and taking other herbs linked to liver dysfunction'. Although the studies in this review did not report liver-related adverse events, the possibility of liver injury is noted as a practice point in this review.

One respondent stated that valerian had widespread global use and was reported to be used in over 800,000 adults in the US in the last 30 days in 2012 (CLARKE, et al., 2015). The TGA notes this was a weighted estimate to the US population from an unknown sample size for the 2012 collection year; data collected between 2002, 2007 and 2012 only had a combined sample of 88,962 adults. It is also not clear how this information is applicable to the Australian population or current use.

According to the 'Rule of three' (Brown, 2017), to detect an adverse reaction with an expected incidence of very rare (<1/10,000), the number of patients needed for an intervention is >30,000. None of the publications cited, individually or collectively comprised this number of subjects. Thus, although liver related adverse events were not reported in the additional publications cited, the number of subjects in individual studies, and collective systematic reviews would not be a sufficient study population to gain an accurate representation of very rare liver related adverse events, also noting that several studies did not collect information regarding adverse events.

Incidence of liver injury

Some respondents noted that there have only been 16 liver-related adverse events associated with valerian in TGA's DAEN from January 1971 – August 2022. Respondents considered this to be a very low count of liver specific events in 51 years and therefore cannot be interpreted as a safety signal requiring a warning statement for valerian.

The TGA notes that spontaneous adverse event reporting cannot be used to estimate the frequency of adverse events due to under-reporting. This is particularly problematic with complementary medicines, which are often considered to be safe and without side effects, and for which liver injury cases may not be reported due to lack of awareness of possible causality by both consumer and healthcare professionals. Notwithstanding, the TGA acknowledges that the overall number of liver injury cases to date presents a degree of uncertainty. Although this is an emerging signal with a limited evidence base, there is sufficient evidence to demonstrate

concern. Importantly the TGA notes that there have been 2 serious cases of liver injury in Australia that involved a sole suspected medicine with valerian as the single active ingredient, both of which required hospitalisation. Another serious Australian case involved a multi-ingredient medicine where valerian was the only ingredient associated with liver injury.

As stated in the consultation document, the TGA is also aware of 57 international reports of drug related liver adverse events associated with valerian, including 27 with valerian as the single suspected medicine. Two fatalities have been reported internationally.

In view of the number of reports of liver injury discussed above, including cases involving serious liver injury, the positive causal association established by expert opinion (NIH LiverTox and ACCM) and TGA clinical assessment/RUCAM analysis, the TGA considers regulatory action is warranted to inform consumers about the risk of liver injury associated with valerian-containing listed medicines. Although the present evidence suggests the risk is very rare, there is sufficient evidence for this emerging concern and for the need for risk mitigation which is particularly important considering valerian is included in a large number of listed medicines available for self-selection and can be consumed without medical supervision.

Comparison to other products that may harm the liver

Unlike listed medicines, the scheduled medicines mentioned by some respondents such as aspirin and paracetamol, are subject to tighter regulatory control than listed medicines. For such medicines the TGA considers the risks and benefits, and requires additional information and controls such as: where and how they can be sold (e.g. in pharmacies), what pack sizes they are available in, specific dosage instructions and what additional information must be provided to consumers (such as label warnings). Aspirin and paracetamol are known causes of dose-dependent liver injury. To mitigate this known risk, several warning statements are required, advising medical supervision for prolonged use such as 'Unless a doctor has told you to, do not use for more than a few days at a time,'; and for paracetamol, 'Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor'. In addition, clear advice on seeking urgent medical advice is provided to consumers if they suspect an overdose. Regarding comparison to some prescription medicines such as flucloxacillin, these medicines are also pre-market assessed by the TGA and require a doctor's consultation and prescription, interaction with a pharmacist, and provision of additional information such as a Consumer Medicine Information leaflet. Furthermore, they are used to treat serious health conditions. These additional increased regulatory requirements ensure these medicines are appropriately regulated to provide an appropriate level of consumer safety.

The TGA does not regulate foods and is not placed to comment regarding the risk of liver injury from consuming foods such as sugar and alcoholic beverages as suggested by one respondent. Food Standards Australia New Zealand (FSANZ) is a statutory authority in the Australian Government Health portfolio and responsible for setting food standards. A whole-of-government consideration of label warnings on self-selected consumer products as suggested by this respondent is outside the scope of this consultation process. There are existing frameworks for foods and therapeutic goods to manage safety concerns with consumer products; any stakeholder concerns with the regulation of food or therapeutic goods can be directed to the appropriate regulatory authority.

Some respondents also noted their concern that the proposed warning statement for valerian is inconsistent with other warnings in the Therapeutic Goods (Permissible Ingredients) Determination. The TGA acknowledges that the proposed warning statement can be revised in order to better communicate the level of risk, and communicate the symptoms of liver injury more clearly and concisely. Any labelling requirements are always assessed on a case-by-case basis and certain previous considerations also included input from various advisory committees that addressed the information available at the time.

Warning statement – length, content, and inclusion of the term 'Warning'

Length of warning statement

The TGA acknowledges concerns around the brevity of warning statements and space on labels for lengthy warning statements and has revised the proposed warning statement to communicate the same intent more concisely.

Referral to nurse practitioners

The TGA notes other healthcare professionals such as nurse practitioners may play a role in diagnosing, assessing, or treating patients who may not have access to a regular doctor. Due to the seriousness of liver injury, accurate and prompt investigation and diagnostic testing is required which needs input from a medical doctor in most circumstances. Noting respondents sought the shortest wording possible for a warning statement, the warning statement will maintain to 'see a doctor' rather than referring to various types of healthcare professionals. Although other wording such as 'seek medical assistance', 'see/contact a medical professional', may be broader, this wording is longer and ultimately achieves the same outcome as 'see a doctor' as other professionals will most likely need to refer patients for review and treatment by a doctor and cause unnecessary delays in early diagnosis. It is expected that in the unlikely circumstance that consumers do not have access to a doctor, that they would seek access to the most appropriate available medical professional for assistance.

Liver injury symptoms

Early signs and symptoms are important so that consumers can take preventative action before late-stage liver injury occurs. It is not appropriate to only list symptoms of liver injury such as jaundice/yellowing of the eyes or skin or dark urine which are symptomatic of late-stage liver injury such as acute liver failure (LiverTox, 2019a). One respondent provided an example of a prescription medication flucloxacillin, that contains a condensed liver warning without reference to detailed symptoms, however these medications are prescribed by medical professionals, and used under medical supervision. Conversely, listed medicines are available for self-selection and administration and patients can access these medications without medical advice and supervision.

Specifically, liver injury from valerian presents as hepatocellular or mixed hepatocellular-cholestatic (LiverTox, 2020). Initial symptoms for hepatocellular liver injury are 'an insidious onset of fatigue and nausea, followed by anorexia, abdominal discomfort (liver discomfort) and then dark urine and jaundice (LiverTox, 2019d).' Symptoms for mixed hepatocellular-cholestatic injury include fatigue and nausea, followed by pruritis, dark urine and jaundice (LiverTox, 2019b).

In order to balance the need for raising consumer awareness of the symptoms of early-stage liver injury but distinguish these from general symptoms (such as digestive discomfort) or expected effects of valerian resulting in a feeling of tiredness, the proposed warning statement has been revised to refer to the symptoms of 'unusual' fatigue, nausea, appetite loss, abdominal pain, dark urine or itching (i.e. pruritis). This allows consumers to observe and assess whether their symptoms are unusual, differ from any regularly experienced symptoms, and if the symptoms are concerning then there is clear advice to stop use and seek medical help accordingly.

The inclusion of the term 'WARNING'

The TGA acknowledges that valerian is a popular herb and based on the current level of evidence, liver injury associated with valerian is very rare. To address the feedback provided, the word 'WARNING' has been removed from the warning statement. The term 'WARNING' has been reserved for strong associations and higher risk situations.

The TGA assessment has identified that the incidence of liver injury associated with valerian is very rare based on the evidence available. The revised warning statement states that liver injury may occur in 'rare' circumstances. This is considered to be the most concise way of communicating the low incidence of liver injury, also noting that in practical circumstances, consumers are unlikely to differentiate between adverse events that are 'rare' versus those that are 'very rare'. Furthermore, combining 'rare' with the words 'may harm the liver', clarifies overall that the occurrence of liver injury is unlikely. The previously proposed wording 'in some people' has also been removed from the statement, noting feedback that this may imply greater certainty and was less informative. With the inclusion of this warning statement, this ingredient is considered to be suitable for use in low-risk medicines. This wording is more concise noting concerns around the brevity of warning statements and space on labels.

Summary

The TGA has not identified a minimum dose, duration of use, processing method of valerian or patient identified risk factors that are established for liver injury to develop. The TGA notes that if symptoms were to occur, then the risk of severe liver injury is mitigated when valerian use is ceased quickly. Although very rare, two expert committees have concluded that there is a causal link between valerian use and liver injury; this is supplemented by the TGA's clinical and RUCAM assessments of several case studies involving valerian use.

Current practice guidelines for idiosyncratic DILI/HILI recommend encouraging patients to report use of herbal supplements to healthcare providers (CHALASANI, et al., 2021). When using self-selected, low risk listed medicines, consumers should be provided with sufficient information of known risks even if they may be rare. This also informs vulnerable populations such as individuals with pre-existing liver problems to make informed decisions about taking certain herbal supplements. The TGA agrees this information should be balanced with the risk of such events occurring.

As discussed above, there is sufficient evidence to warrant regulatory action. The revised warning statement aims to provide clearer advice to consumers, informing them about the possibility of liver injury and symptoms, while noting the very rare incidence of such events occurring.

The TGA will continue to monitor the developing evidence 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. The TGA also intends to raise consumer and health practitioner awareness around the potential for herb induced liver injury generally.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. The 3 ingredients containing valerian will be amended within the Permissible Ingredients Determination commencing on 1 March 2023 to include the following requirements. Sponsors will be provided a 12-month transition period from this time to bring existing listed medicines into compliance.

Affected ingredients

- VALERIAN DRY
- VALERIAN POWDER
- VALERIANA OFFICINALIS

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
VALERIAN DRY		The following warning statement is required on the medicine label when the medicine is for oral use: 'In rare cases, valerian 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.'
VALERIAN POWDER		The following warning statement is required on the medicine label when the medicine is for oral use: 'In rare cases, valerian 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.'
VALERIANA OFFICINALIS		The following warning statement is required on the medicine label when the medicine is for oral use: 'In rare cases, valerian 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.'

Timetable

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

The transition period of 12 months 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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