



Australian Government
Department of Health
Therapeutic Goods Administration

Boxed Warning guidance

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TGA Health Safety
Regulation

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Purpose and scope

The purpose of this guidance is to:

- Outline the objectives for introducing a boxed warning to a Product Information (PI) or Consumer Medicine Information document (CMI)
- Provide guidance on how and when to use a Boxed Warning

The guidance is intended to assist sponsors to understand their obligations and prescribers to understand the rationale for the warning and the magnitude of risk.

Background

The TGA, along with other international medicine regulators, has in place Boxed Warnings as a risk mitigation measure to highlight special warning statements in the PI and CMI to the prescriber and the public. Boxed warnings represent one of the most serious types of warnings that can be mandated by a regulatory agency. More than 30 products on the Australian Register of Therapeutic Goods currently have a boxed warning that has been overseen by the TGA. The boxed warning is a risk mitigation measure that may be proposed by the sponsor or required by the TGA.

International regulatory agencies have taken varying approaches to the use of boxed warnings and they are not used consistently across jurisdictions. In Australia, these warnings are intended to highlight a potential for major impact on public health due to serious adverse events.

Boxed warnings imposed by international regulators, including comparable overseas regulators, are not automatically adopted in Australia, due to differences in approach in different jurisdictions. Boxed warnings by international regulators are considered by the TGA to determine whether any regulatory action is warranted in the Australian context. As part of your obligations as a medicine sponsor, you must notify us when you become aware of the safety actions of a comparable overseas regulatory agency. Further information on your obligations is provided in our guidance on [pharmacovigilance responsibilities](#). The TGA may also be the first jurisdiction to adopt a boxed warning for a medicine.

Pharmacovigilance is defined by the [World Health Organization](#) as the science and activity related to detecting, assessing, understanding and preventing adverse effects and other medicine-related problems. A boxed warning fits into the larger risk management framework alongside other measures.

A boxed warning is a mechanism used to highlight special warning statements in the Product Information (PI) to the prescriber and patient that could significantly alter the risk for patients when prescribed the product. This warning typically concerns a potential for major impact on public health due to serious adverse events that:

- results in death
- is life-threatening
- results in inpatient hospitalisation or prolonged hospitalisation
- results in persistent or significant disability or incapacity
- is associated with a congenital anomaly or birth defect
- is a medically important event or reaction

An adverse event is any untoward medical occurrence in a patient, consumer or clinical investigation subject administered a medicine, and may not necessarily be related to the treatment with the medicine. This includes serious adverse reactions or medical occurrences. However, adverse events that are clearly, or demonstrably, unrelated to the medicine would not be the subject of a boxed warning.

Serious adverse events are included in the special warnings and precautions for use section. A boxed warning is not intended to provide a summary or comprehensive list of all adverse events already captured by warning or precaution statements within the PI.

The rationale for the use of the boxed warning at the beginning of the PI is as a further risk mitigation measure, where the risk associated with taking the medicine cannot be adequately managed or mitigated through inclusion in the special warnings and precautions for use or contraindication sections of the PI.

Required evidence base

Boxed warnings should generally be based on observed data from clinical and sometimes non-clinical sources.

Clinical data may be from:

- Market authorisation studies
- Post-market sources including post-market studies (either sponsor initiated or investigator initiated) and literature or pharmacovigilance activities
- Additional analyses of data
- Off-label use of the medicine (in exceptional circumstances)

Generally, a boxed warning will be required on the basis of direct evidence from the particular medicine. Sometimes a boxed warning may also be required:

- On the basis of indirect evidence or an anticipated effect
- If a particular safety signal occurs for one medicine within a class, but not others.

Typically, a boxed warning would relate to severe identified risks for which there is sufficient evidence that they are caused by the medicine. However, a boxed warning may also be required to manage severe potential risks, for which there is evidence to suspect the possibility of a causal relationship with the medicine, but where there is currently insufficient evidence to conclude that this association is causal. This may include signals associated with a high risk to certain patient groups that have been evaluated with an indeterminate outcome (i.e. which can be neither refuted nor confirmed), a class effect that is plausible for a new medicine, findings from non-clinical studies which have not been observed in clinical studies, or undesirable clinical outcomes observed in clinical trials or epidemiological studies for which there is not yet enough evidence to support a causal relation (e.g. due to low number of events or unexpected incidence rates in comparator groups).

Evidence for a boxed warning that is a class effect could be on the basis of evidence obtained from other products of that class if there are strong mechanistic grounds, including structural characteristics, to expect the same effect. For example, pomalidomide or lenalidomide have a boxed warning for teratogenic effects that was imposed on the basis of effects observed with thalidomide.

The provided evidence requirements are intended to serve as a guideline, but are not prescriptive. It is at the discretion of the TGA to impose a boxed warning statement, where required to manage risks associated with use of the medicine, and this may take into account other types of evidence not listed here. Available evidence will be assessed on a case by case basis. Evidence from off- label use as well as other indirect evidence or anticipated effects may warrant a boxed warning, where causality is not fully established, if the safety concern is serious. In general, more emphasis will be placed on on- label use, but safety signals arising from off- label use may sometimes be relevant for on-label use. Off-label use contributes to understanding of the safety profile and therefore the special warnings and precautions for use section of the PI which may lead to a boxed warning in certain circumstances.

The boxed warning may be amended or removed if further data becomes available that provides evidence against causation. Sponsors may apply for the removal or variation of a boxed warning as part of an appropriate application to the TGA (see process).

The evidence required for removal of the boxed warning should be sufficiently strong, e.g. new well designed study of the medicine in the population at risk or a meta-analysis or new scientific arguments related to the causality of the safety concern.

When a boxed warning is proposed

A Boxed Warning is used alongside other risk mitigation measures such as the [PI](#) wording, [scheduling](#) (e.g. control of access to medicines), [labelling](#) (example of [warning statements on the medicine label](#)), conditions of registration and [post-market pharmacovigilance](#) and other measures including the [Risk Management Plan](#). As per the recent practice a boxed warning is only intended where it is required to manage risk adequately. The following list provides examples of when a boxed warning may be considered, but there may be other circumstances when a boxed warning may also be appropriate:

- An adverse event is identified that is serious and requires a serious warning statement at the beginning of the PI to address the risk associated with a medicine
 - A serious adverse reaction is identified that can be prevented or reduced in frequency or severity by appropriate use of the drug, encompassing:
 - Patient selection (e.g. avoiding or altering use in high risk populations)
 - Patient behaviour or awareness
 - Monitoring (which may be at baseline and/or while on treatment)
 - Avoiding certain concomitant therapies (e.g. because of significant drug-drug interactions)
 - The need for other drugs (e.g. pre-medications)
 - Managing patients in a certain manner (e.g. correct route of administration; correct frequency of use; maximum cumulative dose or clear instructions to avoid serious adverse events)
 - Avoiding use in a specific clinical situation
 - Restrictions to prescribing (e.g. prescription only by a certain class of physician)
- ‘Non-actionable’ reactions (those that cannot be avoided by patient selection, monitoring etc.) may sometimes also require boxed warnings, because drawing clear attention to the particular risk may be important for the clinician, in the discussion of the benefit/risk balance, in informed consent discussions and in considering alternative treatment options.
- There is markedly reduced effectiveness or evidence of net harm in certain patient populations.

Content of the boxed warning in the PI

A boxed warning provides a succinct warning statement, and draws the attention of the prescriber to more detailed information within the main body of the PI. Details of the data sources for the safety issue (e.g. clinical trials, adverse events or precautions) would not routinely be placed in the boxed warning.

The wording of the boxed warning need not be identical to the text of the main body of the PI. Usually, the content of the boxed warning summarises or is drawn from PI text. The medical terminology to describe adverse events in a boxed warning should be consistent with text in other sections in the PI. The boxed warning must reflect content in the main body and is in addition to the main body of text.

The boxed warning should also include:

- Cross-referencing the relevant section of the PI that contains more detailed information.
- Actions to be taken.

Any actions to be performed by the prescriber should be clearly worded in active language at the beginning of the boxed warning. For example 'Do not prescribe to people with impaired renal function'.

Boxed warning and Consumer Medicine Information

The Therapeutic Goods Regulations 1990 (Schedule 12) require the Consumer Medicine Information (CMI) to be consistent with the PI. If a boxed warning is required in the PI, then a similar prominent boxed warning should also be placed at the beginning of the CMI, in a manner that provides sufficient information for a consumer to understand the risks or to prompt a conversation with a healthcare professional. The CMI statement will be directed at the consumer, whereas the statement in the product information is directed at the healthcare practitioner. It may therefore be necessary to include a different level of detail and context within the boxed warning in the CMI. Boxed warning statements in CMI and PI documents will therefore not be identical.

The CMI statement should be:

- In English
- In language that will be easily understood by patients
- Consistent with the statement in the product information
- Of suitable presentation and format
- Actionable for the patient, making them aware of what to do (e.g. ensure that you do not become pregnant, call your doctor if you experience 'effect').

Format of the PI and CMI

Provide the boxed warning in the following format:

- Position the boxed warning at the start of the document so that it is readily and immediately apparent to the reader:
 - PI: the boxed warning should be across the width of the document.
 - CMI: the boxed warning should be in the top left column, or across the width of the document.
- Use a font the same size or larger than the most common font size used in the PI or CMI. Lay out the text to start with the word WARNING or WARNINGS printed in bold capitals in a font no smaller than the font used in the remainder of the boxed warning.
- Arrange so that the text will be surrounded by a continuous rectangle, with a minimum line weight of 1.5 pt.
 - If the line weight is increased, the border width also needs to be increased to maintain readability. A minimum space of 4pt from the text on all sides is recommended.

Process requirements

A boxed warning is part of the PI and CMI documents and is included or changed as part of the pre-market registration and variation processes, or requested as a consequence of post-market pharmacovigilance activities. As a sponsor, you **MUST** meet your [pharmacovigilance reporting responsibilities](#) for all the medicines you have registered on the Australian Register of Therapeutic Goods (ARTG). This includes timely updates of product labels and PI with new safety information.

A boxed warning can be enabled in conjunction with a category 1 or 2 application for the registration or variation to the registration of a prescription medicine or as a safety related variation to a currently registered medicine. The boxed warning in the PI and CMI will be evaluated as part of the [prescription medicine registration process](#) and will be evaluated as part of the PI and your risk management plan (RMP).

You should update your RMP or Australia-Specific Annex (ASA) to document the implementation of a boxed warning. The required timing of submission of the updated RMP to the TGA will largely depend on whether introduction of the boxed warning is associated with other changes to the RMP that require evaluation by the TGA such as changes to the summary of safety concerns, pharmacovigilance plan or additional risk minimisation activities, and will be discussed with you as part of the implementation of the boxed warning.

Refer to '[Risk management plans for medicines and biologicals](#): Australian requirements and recommendations' for guidance, you can contact TGA for advice via (rmp.coordinator@health.gov.au). It should be noted that no changes to existing RMP processes are proposed.

The PI/CMI documents are made available through the TGA website following the approval of the medicine and you must provide updated documents for this purpose:

- PI document(s) approved by the TGA must be lodged with the TGA within 2 weeks of the date of registration of the product(s), and
- Related Consumer Medicines Information (CMI) document(s) must be lodged with the TGA within 2 weeks of the date of registration of the product(s).

We will publish on the TGA website if a new boxed warning is included in the PI.

Changing or removing a boxed warning

A boxed warning is not time-limited and requires a formal application for consideration by the TGA to change or remove the warning.

You may lodge an application with the TGA for a boxed warning to be reviewed if new data on the issue becomes available. You should consider if the new data provides strong evidence against causation and supports a requirement for amendment or deletion of the boxed warning (such as the new information supports inclusion of the information for the adverse event in the precautions/ warning or adverse event section of the PI and CMI only, rather than a boxed warning).

You should apply for changes to a boxed warning by applying to the TGA, the application type will vary depending on the nature of the request (e.g. safety related request to reduce the patient population or add a warning or precaution, or type J change to the Product Information, or other Category 1 application). You may also apply for the removal of a boxed warning via a Category 1 application.

The boxed warning wording may be amended by the TGA based on evidence from sources described on page 5 [‘evidence requirements’](#) or as prescription medicine registration applications for the medicine are approved.

Promotional material

Whereas [advertising prescription medicines](#) to consumers is not permitted under the Therapeutic Goods Act 1989 (the Act), advertising to health professionals is permitted within the [scope of the legislation](#) and is a self-regulatory scheme operated by Medicines Australia.

For prescription medicines that have a boxed warning included in their PI, all promotional material must include the boxed warning or a prominent statement drawing attention to the boxed warning.

A condition of registration will be imposed, that promotional material (other than PI) relating to the registered good must comply with the requirements of the Code of Conduct of Medicines Australia. The condition will apply whether you are a member of Medicines Australia or not.

Abridged PI must accurately reflect the approved PI, including safety-related statements and any boxed warnings that may appear in the Product Information, but may be a paraphrase or précis of the approved PI.

Additional conditions of registration may be imposed as required for a specific risk management approach as part of existing practice and will be on a case by case basis.

Channels of communication

You may be required to undertake additional risk minimisation and communication activities alongside the boxed warning. This is in addition to the requirements for promotional material set out by the Medicines Australia Code of Conduct. Different communication measures may be required depending on the specific circumstance and will be considered as part of the evaluation, on a case by case basis. Consumer and/or healthcare practitioner directed activities may be included as part of the medicine's risk management plan, for example:

- Patient alert cards
- Patient education apps, websites and printed materials
- Healthcare professional education material
- Dear Healthcare Professional letters
- Restricted access or pregnancy prevention programs
- Revising distribution of healthcare professional and patient communication tools

Timelines and implementation

The guidance will come into effect when it is published and applies prospectively where a boxed warning statement is required from the date of registration and not retrospectively for currently marketed products with (or without) existing boxed warnings unless new safety information becomes available that would warrant such a statement or there is a significant discrepancy between boxed warnings in the PI and CMI.

This means that in general, in the absence of new information, changes to an existing boxed warning (e.g. to align the format with this guidance) will not be necessary when there are updates to the PI. An exception to this could be where a class effect is applied to another member of the class. For class specific warnings the TGA would approach sponsors individually to ensure a consistent approach where a boxed warning is required across products of a class. This approach may affect products without a boxed warning at the time.

A boxed warning statement may be requested as part of the registration process, or following registration as part of a post market review of the product. You may also apply to amend boxed warnings for your current product/s. This also applies to biosimilar and biological products as well as to generic products where the innovator or reference product has included a boxed warning. Any amendment or implementation or removal of a boxed warning may be able to be applied to all sponsors' PI documents containing that medicine and indication. The changes for other sponsor's PIs would be required to be submitted through separate applications.

Under the proposed arrangements it should be noted a boxed warning will be consistently included in the PI and CMI to ensure prescribers, dispensers and consumers are aware of the boxed warning.

Version history

Version	Description of change	Author	Effective date
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