Australian Government

Department of Health

Therapeutic Goods Administration

# Boxed Warning guidance

## Public consultation paper

Version 1.0, August 2018

TGA Health Safety Regulation

**Confidentiality**
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

# Contents

# Introduction

## Purpose and scope

The purpose of this paper is to:

- Outline the objectives for introducing a Boxed Warning to a Product Information (PI) document
- Provide draft guidance on how and when to use a Boxed Warning
- Seek feedback from consumers, healthcare professionals and industry on the proposed requirements for Boxed Warnings

This paper focuses on aspects of the Boxed Warning that will inform guidance for industry sponsors intending to, or requested to, include a Boxed Warning statement as part of the Product Information (PI) document. In implementing guidance, we will assist sponsors with determining when a Boxed Warning is required and what it should look like, with a view to ensuring consistency across the prescription medicines regulatory framework.

## Background

Boxed Warnings within the product information document for a medicine represent one of the most serious types of warnings that can be mandated by a regulatory agency as a risk mitigation strategy. More than 30 products on the Australian Register of Therapeutic Goods currently have a Boxed Warning that has been overseen by the TGA.

Boxed Warnings have not only been used in Australia, but are used internationally to draw attention to the most serious of safety issues. Different international regulatory agencies have taken varying approaches to the use of Boxed Warnings and they are not used consistently across jurisdictions, adding to the importance of providing guidance in the Australian context.

# Overview of the proposed Boxed Warning

A Boxed Warning is a mechanism used to highlight special warning statements in the Product Information (PI) to the prescriber. These warnings typically concern prominent safety issues with a potential for major impact on public health. The Boxed Warning is a risk mitigation measure that may be proposed by the sponsor or requested by the TGA. A Boxed Warning is not intended to provide a summary or comprehensive list of all adverse events. These are set out in a special section of the PI for adverse events. Significant adverse events may also be included in the warnings and precautions section. A boxed warning statement is included in addition to this information, at the start of the PI.

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. A warning statement in the Consumer Medicine Information (CMI) which must be consistent with the PI, enhances communication of safety concerns to patients and the general public.

# 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
- Off-label use of the medicine (in certain circumstances)
- Additional studies or independent sources (if sufficiently robust)

A Boxed Warning may be required:

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

Generally, a causal relationship between the medicine and the safety signal that might merit a Boxed Warning should be assessed to be a reasonable possibility. A Boxed Warning may also be required where causality is not fully demonstrated, if the safety issue is of sufficient concern.

The Boxed Warning may be removed if further data becomes available that provides evidence against causation.

**Required evidence to support a Boxed Warning**

Q1: Do you support the proposal for evidence?

a) yes

b) no

c) with modification

Q2: Do you envisage any difficulties with the proposed evidence requirements? Maybe - if a sponsor disagrees with the evidence/interpretation of the evidence.

Q3: What changes to the evidence requirements do you propose to address these difficulties, if any. Open consultation with sponsor (or sponsors for class effect) to evaluate evidence together with the TGA. Also, suggest scope for bracketed information above is better defined.

# When a Boxed Warning is proposed

A Boxed Warning may be appropriate in various situations. The following list of scenarios is not meant to be exhaustive:

- An adverse reaction is identified that is serious relative to the potential benefit of the medicine, and/or not reversible. The likely frequency of the reaction should also be a consideration, although exact frequency data may not always be available.

- 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)
  - 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 in the discussion of the benefit/risk balance and in informed consent discussions.
- There is markedly reduced effectiveness or evidence of net harm in certain patient populations.
- In some circumstances Boxed Warnings may be based on evidence drawn from 'off-label' populations, or the Boxed Warning may refer explicitly to off-label populations, for example if there is a concern about off-label use and the safety concern is sufficiently great.

**When a Boxed Warning is proposed**

Q4: Do you support the proposed circumstances?

a) yes

b) no

c) with modification

Q5: Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed? Difficult to say until it can be applied to a live situation, and then it is a question of how it may affect the sponsor commercially. Also, concerned about off label usage and being stuck with a boxed warning for something that is not promoted.

Q6: What circumstances should be removed, or should additional circumstances be included? Off label should be removed. PIs aren't meant to address off label use. Only information about the registered indication supported by sponsor study.

# Content of the Boxed Warning

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.

**Content of the Boxed Warning in the PI**

Q7: Do you support the proposal?

a) yes

b) no

c) with modification

Q8: What changes would you propose? None.

# Boxed Warning and Consumer Medicine Information

The *Therapeutic Goods Regulations 1990* (Schedule 12) require the CMI to be consistent with the PI. If a Boxed Warning is required in the PI, then a similar prominent Boxed Warning should generally also be placed at the beginning of the CMI, in a manner that provides sufficient information for a lay 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. Boxed Warning statements in CMI and PI documents will therefore not be identical.

The CMI statement should be:

- In English
- Clearly legible
- In language that will be easily understood by patients
- Consistent with the statement in the product information
- Of suitable presentation and format

**Content and Format of the Boxed Warning in the CMI**

Q9: Do you support the proposal?

a) yes

b) no. We believe it has the potential to confuse and overwhelm a patient. If it is already written in the body of the text, maybe

consider a different way to display the AE in the body to highlight its importance.

c) with modification

Q10: Are there other modifications or additions to the proposal you would like to make? Perhaps it should instruct patient to take a closer look at AEs rather than repeat them.

## Format

Provide the Boxed Warning should be presented in the following format:

- Position the Boxed Warning at the start of the PI document so that it is readily and immediately apparent to the reader.
- Use a font the same size or larger than the most common font size used in the PI.
- 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. Go to *Borders and Shading* and then *Options* to increase the spacing to the border. A minimum space of 4pt from the text on all sides is recommended.

**Format of the Boxed Warning in the PI**

Q11: Do you support the proposal?

a) yes

b) no

c) with modification

Q12: What changes would you propose? No.

Q13: Are there other modifications to the proposal you would like to make? No.

## Process requirements

A Boxed Warning is part of the PI document and is instigated or changed as part of the pre-market registration and variation processes, or requested as a consequence of post-market pharmacovigilance activities. The Boxed Warnings, where required, will be implemented in conjunction with new major applications encompassing clinical data or via a condition of registration under Section 28 (2B) of the *Therapeutic Goods Act 1989* (the Act) imposed by the TGA.

The condition of registration will require sponsors to include a Boxed Warning to alert prescribers and patients of the specific risks. The Boxed Warning must be included at the start of the PI, and a patient specific form of the statement must be included in the CMI.

Introduction of a Boxed Warning may require an update to the risk management plan. This is in accordance with existing guidelines on when to submit an updated RMP. No changes to existing RMP process are proposed.

## Changing or removing a Boxed Warning

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

You must lodge an application with the TGA for a Boxed Warning to be reviewed if new data on the issue or adverse drug reaction becomes available, and/or if other risk management tools are proposed. You should apply for changes to a Boxed Warning (e.g. safety related request or type J change to the Product Information), or removal of a Boxed Warning (Category 1 Application).

The Boxed Warning wording may be amended by the TGA based on evidence from reputable sources or as other major applications for the medicine are approved.

**Process requirements**

Q14: Do you support the proposal?

a) yes

b) no

c) with modification. The cost and timing should not create undue burden.

Q15: Do you envisage any difficulties with the proposed process? Yes- Unclear on cost and timeline. Commercial implications.

From a PV perspective - It is unclear what are the timelines/notification by the TGA to Sponsors, eg. If the TGA initiates a boxed warning change, we have 72 hours to notify our partners and other regulatory authorities around the world. When does the clock start?

Q16: Are there other modifications to the proposal you would like to make? Need to consider guidance upfront regarding evidence required to remove a warning. A Cat 1 would be a substantial activity - ? time to approval.

## Promotional material

Two different options are being proposed for the inclusion of Boxed Warnings in promotional material:

### Option 1

- All promotional material must include the Boxed Warning in full.

### Option 2

- All promotional material must include the Boxed Warning in full, OR contain a prominent reference to the Boxed Warning at the beginning of the material.

For both options, brand name reminders would need to include the notation 'See Boxed Warning', drawing attention to the Boxed Warning in the PI.

The proposal described in **Option 2** is similar to requirements set out by industry in the current Medicines Australia Code of Conduct Guidelines (e.g. Section 2 or 3), whereas the requirements outlined in **Option 1** are more stringent.

A specific condition of registration under S28 (2B) of the Act would be imposed for medicines that include a Boxed Warning in the PI. This will require the sponsor to include the Boxed Warning or a reference to the Boxed Warning at the beginning of any promotional material (depending on whether **Option 1** or **Option 2** above is preferred), including any minimum product information as defined in the Medicines Australia Code of Conduct.

Given the range of different mechanisms by which promotional material may be accessed, for example, on mobile devices, print media and computer screens, any requirements around the display of Boxed Warnings would need to be broadly applicable and meet relevant accessibility requirements.

**Promotional material**

Q17: Which of the above options do you support?

a) Option 1. It might get too confusing if it is different to PI (unless its intended for consumer).

b) Option 2

c) Other (please provide details)

Q18: Do you have any suggestions for how Boxed Warnings should appear or be referenced in promotional material (taking into account the different formats and media types which might be used to display this material)?
No.

## Timelines and implementation

The guidance applies prospectively where a Boxed Warning statement is required from the date of registration, and not retrospectively to current marketed products with (or without) existing Boxed Warnings unless new safety information becomes available that would warrant such a statement. A Boxed Warning statement may be requested as part of the registration process, or following registration as a result of post-market pharmacovigilance activities. You may apply to amend Boxed Warnings for your current products if you wish to do so. This also applies to generic products that include a Boxed Warning in line with the brand leader product. Any amendment or implementation or removal of a Boxed Warning may be applied to some or all sponsors' PI documents containing that medicine and indication. As new safety information becomes available, a Boxed Warning may also become relevant to all other sponsors PI documents for the medicine and indication. Changes to multiple PIs would be included through separate conditions of registration.

Following consultation and consideration of stakeholder feedback the finalised guidance is proposed to be published later in 2018 and will take effect immediately.

**Timelines and implementation**

Q19: Do you support the proposal?

a) yes

b) no

c) with modification

Q20: Do you envisage any difficulties with the proposed prospective implementation? For class specific warnings will TGA ask current sponsors to include black box retrospectively i.e. so new ARTG entries aren't disadvantaged?

Q21: Are there other modifications or additions to the proposal you would like to make? As for Q20. Also, perhaps inclusion of how updates will impact other documents, and guidance (eg. timelines, process…) on how sponsors can update impacted documents.

# Version history

| Version | Description of change | Author | Effective date |
|---|---|---|---|
| V 1.0 | Public consultation paper | Prescription Medicines Authorisation Branch | August 2018 |

**Therapeutic Goods Administration**

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

Reference/Publication #