Submission

Consultation: Boxed Warning guidance

August 2018

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INTRODUCTION

The Mylan group of companies, Alphapharm Pty Ltd and Mylan Health Pty Ltd (herein referred to as 'Mylan'), has been supplying medicines in Australia since 1982. We are the leading supplier of medicines by volume to the Pharmaceutical Benefits Scheme (PBS), with about one in six PBS prescriptions dispensed with a Mylan medicine.

Mylan offers locally a broad range of branded, generic and over the counter products - more than 700 individual formulations - and is one of the largest pharmaceutical manufacturers in the country. Last year, our internationally-accredited manufacturing plant at Carole Park, Queensland, produced over 3 billion doses of oral solid dose medicines, more than half of which was exported to about 50 countries.

GENERAL COMMENTS ON THE CONSULTATION

Mylan agrees on having a set guidance regarding when and how a Boxed Warning should be included on a Product Information (PI) and Consumer Medicine Information (CMI). This will aid sponsors, assist prescribers and improve patient safety.

A Boxed Warning should not cause undue anxiety amongst the public, but ensure adequate evaluation by the prescribing or dispensing healthcare professional/s which is of a higher level than other safety information in the PI – with the clear outcome of allowing accurate benefit-risk evaluations per patient.
It is also important to note that key safety information will continue to be placed in appropriate sections of the PI document, which is now standardised in terms of format. The new PI format has allowed the better presentation of safety information and will further support the inclusion of new data as it becomes available.

For this consultation, Mylan believes that it is important to establish a clear definition on the level of safety information a Boxed Warning should contain. A standardised format will ensure a regulated industry standard for future Boxed Warnings with little room for misinterpretation.

Required evidence to support a Boxed Warning?

Question 1: Do you support the proposal for evidence?

c) With modification

Mylan expresses concern regarding the supporting data which is suggested as required for a Boxed Warning to be included to the PI. For example:

- Off-label use of the medicine (in certain circumstances)
  It is likely that the level of off-label use reporting from healthcare professionals and consumers will be low and inaccurate. This may weaken the strength of the Boxed warning and questions the integrity of the reported evidence. It may also be inadvertently promoting off-label use to the healthcare professionals and consumers (especially if the Boxed Warning is to be included to the CMI).
- Post-market sources
  There should be a standardised level of robustness on Post-market sources before a Boxed Warning is instituted. Further if incorporated, this should also ensure that should post-market sources refute a Boxed warning this is reviewed with the same due diligence or urgency.
- Indirect evidence or an anticipated effect (e.g. a class effect):
  Where causality is not fully demonstrated, or the warning is based on "anticipated" effect, the Boxed Warning should have an expiry date. This gives the sponsors an opportunity to monitor and gather evidence to establish whether the Boxed Warning is justified, or refute the Boxed Warning within the given timeframe. (Black Triangle Scheme).

Mylan requests that the TGA establish guidelines on the evidence requirements, especially regarding the robustness of the evidence, required to add and remove a Boxed Warning. The challenges in assessing risk based on limited information available for new medicines or indications is acknowledged, and it is anticipated that robust safety considerations will continue to be made in this field.

Question 2: Do you envisage any difficulties with the proposed evidence requirements?

Boxed Warnings, being the most serious form of warning required by a medicine, have a significant impact on a physician's prescribing pattern. It may also impact a patient's disease state management based on the healthcare providers risk/benefit decision, depending on media coverage.

As mentioned above, the main difficulty will be to establish robustness of evidence to ensure that the Boxed Warnings are sparingly and meaningfully published. Noting that at present, the type of evidence that is required to disprove or remove a Boxed Warning is held to a higher level of robustness and reliability. Mylan believes that similar principals should be followed to request the addition or removal of a Boxed Warning to be added to both a PI and CMI, while recognising that patient safety is paramount.

It is suggested that results of the Black triangle scheme (5 years' worth of reported data) should be able to be used as evidence to remove boxed warnings.

Question 3: What changes to the evidence requirements do you propose to address these difficulties, if any?

Mylan disagrees with a Boxed Warning that is related to off-label use. Any warnings related to off-label use should be discussed in Section 4.4 Special Warnings and Precautions section of the PI.

Also, for "indirect evidence or an anticipated effect (e.g. a class effect)", there needs to be a specified set of data that indicate a valid reason for the Boxed Warning to be applied to all medicines in that class.

Mylan supports a guideline on the severity and frequency of Adverse Events / Adverse Drug Reactions prior to addition of a Boxed Warning.

When a Boxed Warning is proposed

Questions 4: Do you support the proposed circumstances?

b) No

Mylan believes it is important to limit the use of a Boxed Warning to medicines which have shown significant (or highly unexpected) risks of fatal or serious, debilitating and/or permanent adverse events, to maintain the strength and impact of the warning.

Question 5: Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed?

The proposed list of circumstances would ensure the following types of medicines to have a Boxed Warning:

- All cytotoxic medicines – need for premedication, risk of exposure, patient management
- Narrow Therapeutic Index medicines – requirement for monitoring

Mylan is concerned if Boxed Warnings are used too frequently, there is a risk of the message being diluted amongst healthcare professionals to a point where the box no longer draws the desired attention.

Question 6: What circumstances should be removed, or should additional circumstances be included?

Mylan believes that, the use of Boxed Warnings should be limited to a medicine's significant (or highly unexpected) risks of fatal or serious, debilitating and/or irreversible adverse events. The PI in entirety should be viewed as a tool for communication of risk and benefit, and used to guide prescribing practice. Ultimately the decision to prescribe belongs to the treating healthcare professional however Mylan's aim is to ensure all relevant information is presented in an accurate and balanced format to ensure appropriate decisions can be made regarding patient care.

Content of the Boxed Warning in the PI

Question 7: Do you support the proposal?

a) Yes

Question 8: What changes would you propose?

Mylan believes the Boxed Warning should succinctly capture the circumstances where the patient is at risk of fatality or serious, debilitating and/or irreversible adverse events, which alerts and encourages the healthcare professionals to read the PI in detail before prescribing.

The message should be succinct. It should not include any detailed explanations inside the box, for example referencing statistical results from clinical trials, recommended screening etc. A large block of text introduces the risk of diluting the main message and lowering the impact of the main Warning.

Content and Format of the Boxed Warning in the CMI

Question 9: Do you support the proposal?

a) Yes

Mylan agrees with the TGA proposal, which is in line with the current requirements where the CMI is required to be consistent with the PI.

Question 10: Are there other modifications or additions to the proposal you would like to make?

It should be clarified that the CMI Boxed Warning should be worded to inform a patient, not to deter a patient from taking the medicine. The Boxed Warning should be short and impactful, written in colloquial language which encourages a conversation with the healthcare professional to make an informed decision.

Format of the Boxed Warning in the PI

Question 11: Do you support the proposal?

a) Yes

Mylan agrees with the format that the TGA has proposed

Question 12: What changes would you propose?

N/A

Question 13: Are there other modifications to the proposal you would like to make?

No.

Process requirements

Question 14: Do you support the proposal?

a) Yes

Mylan supports the proposed implementation of the Boxed Warnings in conjunction with new major applications or as a condition of registration imposed by the TGA, where a Boxed Warning is deemed necessary. The wording of the Boxed Warning should be discussed and agreed by both the sponsor and the TGA.

Question 15: Do you envisage any difficulties with the proposed process?

Mylan does not anticipate difficulties with the proposed process. As per normal evaluation process, the sponsors should be given opportunities during the evaluation period of a major application to refute/justify the requirement of a Boxed Warning.

Question 16: Are there other modifications to the proposal you would like to make?

Mylan believes that sponsors should be able to use a wider range of references and supporting evidence when applying to remove an existing Boxed Warning, using the same principles for instituting the Warnings to the PI initially.

For example, for new chemical entities with a Boxed Warning that is also under the Black Triangle Scheme (where adverse events are closely monitored for 5 years after registration), the sponsors should be able to use the reported ADR data to justify removing the box and relocating the information to the appropriate section of the PI.

Promotional material

Question 17: Which of the above options do you support?

c) Other (please provide details)

As discussed in “Content of the Boxed Warning in the PI” section above, the Boxed Warning should only contain a succinct summary of the warning. If boxed warnings can be expressed succinctly, Mylan supports Option 2 having the Boxed Warning in full, or having a prominent reference to the Boxed Warning.

However, if there are difficulties in minimising the detail of the Boxed warning, Mylan supports having the option to include a condensed version of the warning in the Minimum PI.

Question 18: 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)?

Mylan suggests placing the Boxed Warning in a textbox directly above the body of minimum PI text. For promotional materials that do not require a minimum PI, (e.g. trade display for healthcare professionals) a short text box stating, "This product has a Boxed Warning" or similar can be placed on the material, with adequate prominence (e.g. in close proximity with the recommendation to review the PI before prescribing).

Timelines and implementation

Question 19: Do you support the proposal?

a) Yes

Question 20: Do you envisage any difficulties with the proposed prospective implementation?

Mylan does not anticipate difficulties in implementation timelines, provided that the suggestions regarding boxed warnings made in this Consultation response are considered.

Question 21: Are there other modifications or additions to the proposal you would like to make?

No.