30 August 2018

Transparency Reforms and Evaluation Support Section
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Dear Sir/Madam

Re: Consultation: Boxed Warning Guidance

Thank you for the opportunity to comment on this proposed guidance.

Overview

The need for Boxed Warnings in Australian Product Information (PI) for prescription medicines is not new. In 1995 the then Australian Drug Evaluation Committee (ADEC) identified the need and passed a resolution (No.5666; Attachment 1).

> RESOLUTION NO. 5666
>
> A MECHANISM FOR HIGHLIGHTING SPECIAL WARNING STATEMENTS ABOUT ADVERSE DRUG REACTIONS IN THE PRODUCT INFORMATION (BOXED WARNINGS) SHOULD BE IMPLEMENTED. SUCH WARNINGS SHOULD APPLY ONLY TO LIFE-THREATENING OR SERIOUS AND/OR UNEXPECTED ADVERSE REACTIONS AND SHOULD BE INSTITUTED ON THE ADVICE OF THE ADEC ONLY AFTER DUE CONSIDERATION OF THE SERIOUSNESS OF THE REACTION AND THE LIKELY THERAPEUTIC IMPLICATIONS OF CHANGES IN PRESCRIBING PROMPTED BY THE WARNINGS.

Gilead is of the view that this guidance from the ADEC remains as valid today as it did in 1995. The current proposed guidance from TGA has potential to drastically expand the implementation of Boxed Warnings for safety concerns far broader and less significant than the "serious and/or unexpected adverse reactions" of concern to the ADEC. There is a significant risk that wider use of Boxed Warnings to less significant issues will lead to a dilution of the effectiveness this type of warning, a warning whose effectiveness is based largely on being unusual and highly prominent at the start of the PI.

Most concerning of all would be the application of a Boxed Warning based upon an anticipation of a class effect. It is our position that Boxed Warnings should only ever be applied based upon direct evidence not supposition. And as noted originally by the

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ADEC they should “apply only to life-threatening or serious and/or unexpected adverse reactions”.

That said, Gilead agrees that implementation of Boxed Warnings by TGA could be improved and clearer guidance to sponsors as well as TGA personnel is required.

Personally I have professional experience working with sponsored medicines where unique unexpected adverse events truly warranted Boxed Warnings: lamotrigine and rash, abacavir and hypersensitivity, for example. Unfortunately I also recall examples when applications of Boxed Warning were, in my opinion, unwarranted: enoxaparin sodium regarding use in pregnancy and an oncology medicine associated with increased risk of death from infection when the vast majority of medicines in this field have this risk - but very few have a Boxed Warning. Inconsistent application of Boxed Warnings has a profound effect in suggesting one medicine is inherently less safe than others in their class which may be untrue. In the case of enoxaparin sodium the medicine became widely used by physicians in pregnant patients despite the Boxed Warning and eventually the Boxed Warning was removed. The enoxaparin sodium case highlights the unintended consequences of making a Boxed Warning based on a hypothetical risk where in reality the new therapy is very different to older therapies; eventually leading physicians to ignore the Boxed Warning and thereby undermining the credibility and reliability of the Boxed Warning and Australian PI in general in the eyes of prescribers.

Expectations of class effect can justifiably be used to create precautionary statements in the PI in the absence of any direct evidence. Physicians do need to be advised of potential risk, but to the ADEC’s point, due regard should be given to “the likely therapeutic implications of changes in prescribing prompted by the warnings”. A Boxed Warning as the highest level of warning in the label should be very carefully applied and should only be based on clear evidence. Suggesting class warnings in absence of evidence has the potential long-term consequence of preventing patients being prescribed newer, safer and more efficacious medicines because their safety profile is deemed similar to current therapies without evidence. In 2002 when tenofovir disoproxil fumarate was registered for the treatment of HIV it came with class warnings regarding lipodystrophy and lactic acidosis - despite not being observed in clinical trials - as these were important observed side effects with other HIV treatments of the day. Over the years physicians became familiar with the medicine and no longer saw these adverse events and ignored the warnings in the PI. Almost 2 decades later, these hypothetical warnings have only recently been removed from the PI of some tenofovir disoproxil fumarate containing HIV medicines. It is easy to suggest a hypothetical risk may exist; it takes decades to prove it doesn’t. If, in 2001, these warnings had been imposed as a Boxed Warning – as would be possible if the proposed guidance were applied at the time – the therapeutic implications of retaining patients on far less safe and efficacious HIV treatment options would have been profound.

The ADEC resolution makes an important point; Boxed Warnings should be “subject to a flexible mechanism of review of their continued validity”. The final guidance on Boxed Warnings should include what evidence has been found acceptable by TGA in the past to remove Boxed Warnings from Australian PIs and provide this as guidance to sponsors on how to remove them where no longer valid.

Response to Questions in Consultation Document:

Required evidence to support a Boxed Warning

Q1: Do you support the proposal for evidence?

a) yes
b) no
c) with modification

With modification.

Q2: Do you envisage any difficulties with the proposed evidence requirements?

A Boxed Warning as the highest level of warning in the label should be very carefully applied and should only be based on clear evidence.

Q3: What changes to the evidence requirements do you propose to address these difficulties, if any?

A Boxed Warning should not 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.

When a Boxed Warning is proposed

Q4: Do you support the proposed circumstances?

a) yes
b) no
c) with modification

No.

Q5: Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed?

The current proposed guidance from TGA has potential to drastically expand the implementation of Boxed Warnings for safety concerns far broader and less significant than the "serious and/or unexpected adverse reactions" of concern to the ADEC (Resolution 5666). There is a significant risk that wider use of Boxed Warnings to less significant issues will lead to a dilution of the effectiveness this type of warning, a warning whose effectiveness is based largely on being unusual and highly prominent at the start of the PI.

Many of the proposed situations apply to a high proportion of current medicines. It highlights the overarching broadness of these listed situations that, under this guidance it would be reasonable that:

- Many antiviral and anticonvulsant medicines have a Boxed Warning regarding interaction with St John's Wort; and

- Virtually all chemotherapeutic agents have a Boxed Warning regarding restriction to specialist prescribing and the need for pre-medications.

This section is written in the wrong context. The reason for the Boxed Warnings is a serious risk in using the medicine. How that risk is prevented or reduced is irrelevant to when it may be required. e.g. The risk is not the need for other drugs, the risk is a potential serious adverse event seen without use of the other drugs.

The second, third and fourth bullet points are related to risk mitigation not "When a Boxed Warning is proposed" and should be moved to "Content of the Boxed Warning".

Virtually all medicines have potential 'serious' adverse reactions. This section should be written succinctly stating just how serious an adverse event must be to justify this highest level of warning. It would be helpful to provide examples of current medicines approved by TGA with a Box Warning and provide commentary as to why this is the case. Unequivocal cases such as thalidomide and methotrexate are obvious but others that convey differing concerns would be helpful.

Q6: What circumstances should be removed, or should additional circumstances be included?

See answer to Q 5. Boxed Warnings should only be applied to life-threatening or serious and/or unexpected adverse reactions. The circumstances of how these reactions manifest or are controlled are not relevant to this section.

<u>Content of the Boxed Warning in the PI</u>

Q7: Do you support the proposal?

a) yes
b) no
c) with modification

Yes.

Q8: What changes would you propose?

None.

Content and Format of the Boxed Warning in the CMI
Q9: Do you support the proposal?

a) yes
b) no
c) with modification

Yes.

Q10: Are there other modifications or additions to the proposal you would like to make?

No.

Format of the Boxed Warning in the PI

Q11: Do you support the proposal?

a) yes
b) no
c) with modification

Yes.

Q12: What changes would you propose?

None.

Q13: Are there other modifications to the proposal you would like to make?

No.

Process requirements

Q14: Do you support the proposal?

a) yes
b) no
c) with modification

Yes.

Q15: Do you envisage any difficulties with the proposed process?

As noted in the overview to this response, it is inherently difficult to prove safety to remove a Box Warning once in place. It is easy to suggest a hypothetical risk may exist; it takes decades to prove it doesn't. Therefore they need to be applied only where truly required (to avoid diluting the effectiveness of the tool) and should be based on actual data and not perceived class effects.

Q16: Are there other modifications to the proposal you would like to make?

No.

Promotional material

Q17: Which of the above options do you support?

a) Option 1
b) Option 2
c) Other (please provide details)

Option 2.

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)?

The Boxed Warning should appear as part of the Minimum PI in promotional materials wherever the Minimum PI is required.

Timelines and implementation

Q19: Do you support the proposal?

a) yes
b) no
c) with modification

No. Revised guidance following consultation may be markedly different to current proposed or fail to address the concerns of stakeholders, so immediate implementation seems unreasonable.

Q20: Do you envisage any difficulties with the proposed prospective implementation?

The use of Boxed Warnings is currently in place without this explicit guidance. There seems little need to rush immediate implementation. More time should be taken on consultation with stakeholders.

Q21: Are there other modifications or additions to the proposal you would like to make?

As noted in the overview and in response to TGA questions above, there is a need for greater clarity on what constitutes a serious and/or unexpected adverse reactions that warrants a Boxed Warning. There is a significant risk that wider use of Boxed Warnings to less significant issues will lead to a dilution of the effectiveness this type of warning, a warning whose effectiveness is based largely on being unusual and highly prominent at the start of the PI.

Overall the guidance is too broad. Boxed Warnings should be exclusively reserved for use only to life-threatening or serious and/or unexpected adverse reactions. Boxed Warnings should only be based on clear evidence.

Yours sincerely

Andrew Notley
Associate Director Regulatory Affairs

Attachment 1:

RESOLUTION NO. 5666

A MECHANISM FOR HIGHLIGHTING SPECIAL WARNING STATEMENTS ABOUT ADVERSE DRUG REACTIONS IN THE PRODUCT INFORMATION (BOXED WARNINGS) SHOULD BE IMPLEMENTED. SUCH WARNINGS SHOULD APPLY ONLY TO LIFE-THREATENING OR SERIOUS AND/OR UNEXPECTED ADVERSE REACTIONS AND SHOULD BE INSTITUTED ON THE ADVICE OF THE ADEC ONLY AFTER DUE CONSIDERATION OF THE SERIOUSNESS OF THE REACTION AND THE LIKELY THERAPEUTIC IMPLICATIONS OF CHANGES IN PRESCRIBING PROMPTED BY THE WARNINGS.

BOXED WARNINGS SHOULD BE:

APPLIED PROSPECTIVELY ON A CASE BY CASE BASIS

SUCCINCT AND DESIGNED TO DRAW THE ATTENTION OF THE PRESCRIBER TO INFORMATION WITHIN THE MAIN BODY OF THE PRODUCT INFORMATION. THE WORDING OF THE BOXED WARNING NEED NOT BE CONFINED TO THE TEXT OF THE APPROVED PRODUCT INFORMATION.

PLACED ON THE PRODUCT PACKAGING WHEN JUSTIFIED ON AN INDIVIDUAL BASIS.

APPLIED IN FULL TO ALL ADVERTISEMENTS (FULL, ABRIDGED OR SHORT) AND TO BRAND NAME REMINDERS IN SOME FORM OF UNIVERSAL NOTATION, LOGO OR SYMBOL.

SUBJECT TO A FLEXIBLE MECHANISM OF REVIEW OF THEIR CONTINUED VALIDITY.

AS A GENERAL PRINCIPLE, THE <u>ADEC WOULD WISH TO BE INVOLVED IN THE CREATION OF THE WORDING OF BOXED WARNINGS</u>.