Transparency Reforms and Evaluation Support Section
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
DUE DATE: 31 August 2018

Dear Sir/Madam

Boxed Warning Guidance

Medicines Australia (MA) welcomes the opportunity to provide comment on the Therapeutic Goods Administration (TGA) consultation paper 'Boxed Warning Guidance'.

Our submission has been prepared with the expert input of MA's Regulatory Affairs Working Group (RAWG) and its Expert Advisory Group on Pharmacovigilance. Members are selected for their regulatory and pharmacovigilance experience and industry knowledge, and bring a whole-of-industry perspective to the consideration of regulatory issues that stand to impact to our sector.

MA considers that Boxed Warnings are one of a number of approaches that can be utilised as part of an overall risk management strategy to highlight to healthcare professionals the importance of quality use of medicines to ensure patient safety and optimise clinical outcomes. However, it may not be the most appropriate tool to communicate and mitigate potential risk, therefore it cannot be considered in isolation. Any guidance on Boxed Warnings must therefore be viewed in a broader context of more contemporary enhancements to the TGA medicines PV framework designed to proactively minimise, detect and address medicine safety-related issues. For instance, the introduction of risk management plans (RMPs) that set out the required actions a sponsor must undertake are a far more effective and comprehensive means of addressing specific major risks for a specific medicine or class of medicine. The option to propose measures other than a Boxed Warning should thus be available to Sponsors if they can demonstrate that these measures can effectively address the specific risk.

With the recent introduction of the Black Triangle Scheme that highlights the need for robust pharmacovigilance for newly approved medicines, it is important that both healthcare professionals and consumers are educated on the purpose of each scheme as there may be confusion on the differences between the two. This will avoid creating undue alarm about the safety of a medicine which could lead to non-adherence to physician decisions on prescribed treatments or cause prescribers to cease prescribing a medicine with a Boxed Warning or black triangle, which in turn may have consequential impacts on patient health outcomes.

On the basis of the above considerations MA does not support a separate guidance on boxed warnings but considers it should be integrated as part of the existing guidance relating to Risk Management Plans and/or Prescribing Information.

Our detailed feedback on the guidance, is contained in Attachment 1, including answers to the specific questions included in the consultation paper and is based on consideration of the following:

- Is the guidance sufficiently clear and easy to follow?
- Are there any aspects that are not currently covered in the guidance?
- Are there any other issues that may affect the usability of the guidance?
- Are there any major issues relating to the content of the guidance that are likely to affect Industry?

Our response includes suggestions for changes to provide better clarity on requirements which will support practical implementation as well as identifying any areas of concern.

We would be happy to discuss or provide further comment on any aspect of our response and we would appreciate being kept up to date on further developments.

For further correspondence on this matter, please contact Betsy Anderson-Smith on banderson-smith@medaus.com.au

Yours sincerely,

Elizabeth de Somer
CEO, Medicines Australia

Attachment 1 - Consultation: Boxed Warning Guidance

Page	Item	Comments and Rationale
-	**General Comments** Medicines Australia **does not support** development of a separate Boxed Warning guidance document by the TGA	• The decision to implement a Boxed Warning needs to be taken considering all relevant risk mitigation measures that can used to convey important safety information to healthcare professionals and patients. Therefore it should not be considered in isolation but form part of existing Risk Management or Product Information guidance • TGA needs to undertake an educational program directed towards healthcare professionals and consumers that aims to inform them of the general significance of a Boxed Warning in a Product Information (PI) and Consumer Medicine Information (CMI) to ensure it does not cause unnecessary alarm or inappropriate changes in prescribing and usage patterns. This should be undertaken as part of a broader exercise to improve safety reporting that also facilitates understanding of the Black Triangle Scheme and differences between the two approaches • The guidance will be targeted too widely if it is intended to be a document for the public, healthcare professionals and industry/sponsors.
5	**Required evidence base**	
Q1	Do you support the proposal for evidence? ~~Yes/No/~~**With modification**	MA supports the proposal for evidence with modification. • The evidence used to determine whether a Boxed Warning should be included in the PI should be robust and reflect vigorous data collection.
Q2	Do you envisage any difficulties with the proposed evidence requirements? **Yes**	The evidence for a Boxed Warning should be at least as rigorous as the evidence used to form the rest of the PI document. All PI wording is carefully formed based upon robust evidence and reviewed thoroughly by both the Sponsor and the TGA. The level of evidence for a Boxed Warning should not be any lower than any other sections of the PI, and particularly so, as it is the most prominent section of the whole document. The proposal as written does not provide a well-defined evidence base reflective of the need for a risk assessment to be conducted and the premise that Boxed Warnings should be of high impact and low frequency to ensure that increased caution is taken. ▪ "Additional studies or independent sources" requires further definition on what would be considered sufficiently robust. ▪ Evidence from Post Marketing data sources must be robust and a causal relationship must be established prior to consideration of a Boxed Warning due to the nature of many confounders in post marketing reporting. ▪ Off-label use should not be utilized as an evidence source as it is especially

Page	Item	Comments and Rationale
		difficult to manage since healthcare professionals are generally reluctant to report AEs suspected to have occurred in patients taking a medicine for an unapproved use. This will make it difficult for sponsors to generate evidence that may eventually support the removal of a warning against off-label use. ▪ It should be transparent to the sponsor and clinicians on how the data from independent sources will be assessed as the basis for issuing a Boxed Warning. There could be a potential for under or over translating evidence from off label use or data from independent sources in the absence of more structured guideline. Lack of a standard approach may lead clinicians to question the accuracy and utility of the warning. ▪ MA asserts that causality should be established, i.e., the Boxed Warning should relate to a serious adverse drug reaction rather than an adverse event. Therefore, the sentence that there should be 'a reasonable possibility' should be amended in the guidance. ▪ Additional information or examples should be given to clarify the tipping point for causality not being "fully demonstrated" and a safety issue of "sufficient" concern.
Q3	What changes to the evidence requirements do you propose to address these difficulties, if any?	• Boxed Warnings should be used for serious warnings that cannot be adequately covered under Precautions or Contraindications when alternative risk mitigation measures are deemed less effective • The criteria for accepting and assessing evidence from additional studies and data from independent sources should be clearly described to avoid inappropriate evidence translation • Principles of pharmacovigilance management should be applied to the evidence required underpinning the requirement for a Boxed Warning. ▪ A signal must have been detected and causality assigned ▪ 'Post-market sources' should be replaced with 'post-market studies'. ▪ 'Off-label use of the medicine (in certain circumstances)' should be removed. ▪ 'Additional studies or independent sources (if sufficiently robust) should be replaced with 'Sponsor/TGA pharmacovigilance databases'.

Page	Item	Comments and Rationale
5	**When a Boxed Warning is Proposed**	
Q4	Do you support the proposed circumstances? ~~Yes/No/~~**With modification**	• MA supports the proposed circumstances, with modification. • A Boxed Warning should only be included in the PI for products that have/are associated with specific safety problems, whose clinical importance or severity are considered to have a critical impact on patient welfare and where alternative risk mitigation strategies are deemed less effective. The impact of the Boxed Warning should not be diluted through overuse. A Boxed Warning should be used as an exception, rather than routinely to ensure the significance is understood and signal that increased caution is required. For example, the FDA guidance states that a Boxed Warning, highlights to prescribers, an adverse reaction that could be, fatal, life threatening or permanently disabling. Thereby alerting the prescribers to the essential need to assess the risks and benefits of using the drug. • Consistent language should be used throughout the guidance so that the purpose of a Boxed Warning is more precise and unambiguous. For example on Page 4 under Background and Overview, there are several different descriptions on the purpose of a Boxed Warning e.g. 'most serious types of warnings', 'most serious of safety issues', 'highlight special warnings', 'concern prominent safety issues'. • To provide details of the Boxed Warning in an off-label setting could be perceived as endorsement to use the product for that indication. Regardless of the presence of a Boxed Warning, if a healthcare professional determines to use a product off-label then caution should be employed.
Q5	Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed?	• To be useful, the TGA guidance should distinguish between information required for a Boxed Warning versus Warnings and Special Precautions for Use, and specifically what would trigger the elevation of a warning/special precaution into a Boxed Warning. • The proposal suggests there will be increased use of Boxed Warnings as the threshold for inclusion appears to have been reduced from that currently in place, which will dilute the impact the Boxed Warning should have. Boxed Warnings should not be used in place of other risk mitigation measures where such measures will be effective. • There is no definition for serious side effects. This list is too long and vague and

Page	Item	Comments and Rationale
		covers everything that should be and can reasonably be placed under Precautions section of the PI. It may lead to inclusion of some of the less serious conditions as a Boxed Warning. The wide use of Boxed Warnings makes it very difficult for physicians to know what is important and what is really important." It will also discourage them to prescribe the medicine or on the contrary make them to ignore and underestimate the warning. • A significant challenge will be the consistency of application of the guidance by TGA Delegates based on the significant flexibility on what may be judged as appropriate circumstances to warrant a Boxed Warning. All of the circumstances described in the guidance for requiring a Boxed Warning equally apply to the Warnings and Special Precautions for Use section of the PI. • In some instances the Boxed Warning may not be the most appropriate tool to communicate and mitigate potential risk, therefore it may not be easy to categorically state in which situations a Boxed Warning is required. Proposed circumstances need to be realistic and should be used as a "guide" rather than a "must have" and the product would need to be assessed on a case by case basis. • For instance, the risks and harms associated with products containing isotretinoin, an active ingredient known to cause major human fetal abnormalities, have been managed through mechanisms other than the use of a Boxed Warning in the PI, such as strongly worded contraindications and warnings/precautions in the PI, alerts on packaging and education programs. • In some situations, the provision of targeted educational material to prescribers would more appropriately address safety concerns. Proposed educational material can be developed to mitigate the particular risks and appropriately inform prescribers of these risks. Sponsors can assess the effectiveness of this educational material via a survey. The survey would aim to assess the physicians' knowledge and understanding of the educational material, how to effectively prescribe the particular product and manage patients at risk while on therapy. • Inclusion of 'Non-actionable' reactions in a Boxed Warning without direction for management of the reaction dilutes the meaningfulness of a Boxed Warning

Page	Item	Comments and Rationale
		• In situations where disparity exists amongst regulators where one HA may enforce a Boxed warning and others may not, this may have an impact on physicians' prescribing preferences and differences in decision-making in weighing the benefits and risks for patients. In addition, although it is assumed that due to its prominent placement, a Boxed Warning may draw the attention of the prescriber to information within the main body of the PI, there are mixed opinions as to the effectiveness of Boxed Warnings in risk mitigation in clinical practice. Some studies have shown that these Boxed Warnings may not be adhered to in clinical practice (Forbes et al, 2016; Wagner et al, 2006). It has also been demonstrated that a Boxed Warning does not increase a physician's ability to assess the risk/benefit ratio of a specific treatment for an individual patient, nor is not necessarily true that a physician and patient will have a conversation about a medicine's Boxed Warning (Shah et al, 2010). Shah et al (2010) state "FDA warnings do not provide adequate guidance for providers about how to incorporate the warning into clinical decision making. Warnings can be interpreted in a variety of ways, and patient protection may be inconsistent as a result".
Q6		• The list can be summarised in a more concise way similar to the approach used in the FDA guidance to provide clearer direction o Potentially **life threatening or permanently disabling** adverse reactions which outweigh the benefits. o There is a serious reaction that can be prevented or reduced in frequency or severity by patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patient in a specific manner, or avoiding use in a specific clinical situation. o Restrictions on use and distribution are needed to assure safe use.
6	**Content of the Boxed Warning**	
Q7	Do you support the proposal? ~~Yes/No~~/**With modification**	• The Boxed Warning should be succinct and refer the reader to the body of the PI. The recently implemented reformatting of the PI in Australia, now enables easier location of critical information. If the Boxed Warning appears fully comprehensive,

Page	Item	Comments and Rationale
		it creates the risk that the reader may not feel it necessary to review the rest of the PI where critical information on the safe and effective use of the medicine is described. • When the frequency of events in a Boxed Warning is described the terminology used should be aligned with international standards, i.e. CIOMS. Additionally, the summarising of text in the Boxed Warning should not be so ambiguous that the warning can then be interpreted to be something different or separate to content in the body of the PI. • Medical terminology to describe AEs in a Boxed Warning should be consistent with text in other sections in the PI, e.g. use of words such as common, or rare.
Q8	What changes would you propose?	• There should be a single format and a structure to be used for consistency across the industry rather than options. • Should be cross referenced to the appropriate section of the PI. • Sponsors should be given the option of proposing a modification to the content of the boxed warning if they can demonstrate that drawing attention to, and managing a specific risk can be done through other means such as targeted prescriber communication and education programs
7	**Boxed Warning and Consumer Medicine Information**	
Q9	Do you support the proposal? **Yes/No/With modification**	• MA does not support the proposal for the Boxed Warning statement at beginning of the CMI with modification. The decision to prescribe a product for an individual patient is at the discretion of the treating physician in consultation with their patient. The physician has access to the full information contained within the Product Information, and as such is the appropriate person to discuss any safety concerns with the patient as necessary at the time of the prescription being written and prior to the prescription being filled. Whilst pharmacists may have the opportunity to discuss the Boxed Warning with the consumer, they may not fully understand the clinical risk benefit assessment in an individual patient and the full evidence underpinning the decision-making of the prescriber. • Inclusion of the proposed statement in CMI is likely to cause alarm and/or prescribed medicines not to be taken as directed, and as such not contribute to

Page	Item	Comments and Rationale
		the quality use of medicines. • A standard sentence should be used to introduce all Boxed Warnings in the CMI. This sentence would convey the overarching message to talk to your doctor about the following special risks with the product. • From a formatting and patient understanding viewpoint, where a product also has a black triangle, a Boxed Warning may cause additional confusion.
Q10	Are there other modifications or additions to the proposal you would like to make?	• MA supports inclusion of meaningful warnings, cautions and patient actions in the CMI in the appropriate CMI sections (as detailed by CMI guidelines). Research and testing of CMIs with patients has shown that there are better outcomes if information on side effects are grouped together and warnings and precautions are placed in consistent locations across all CMIs so information can be found easily. • More information/context is necessary than what may be required for healthcare professionals. • Where possible, the information for patients should be "actionable" (stop the drug, or call your doctor if you experience x, y or z). • Patient language will need careful consideration due to highly heterogeneous levels of health literacy in the general public. Language should also not alarm patients with the potential for medication non-compliance. Language which directs the patient to discuss an appropriate issue rather than state the issue alone may be more appropriate. • Boxed Warnings should only be included in the CMI if causality has been established for a strong warning and should be communicated in simple, clear language. • A study by Moeller et al (2010) assessed the awareness of Boxed Warnings amongst a selection of American pharmacy students. The researchers concluded that the awareness of Boxed Warnings was proportional to the education level of the student. Therefore, it is possible that Boxed Warnings may not be well understood by some Australian consumers. This is particularly important for complex disease states where patients may be faced with complex health care decisions, and could find the information in a CMI overwhelming (Tong et al). Boxed Warnings are relatively infrequent in Australian CMIs and may be poorly understood by patients.

Page	Item	Comments and Rationale
8	**Format**	
Q11	Do you support the proposal? **Yes**	MA supports the proposal.
Q12	What changes would you propose?	The format is acceptable and no changes to format are proposed.
Q13	Are there other modifications to the proposal you would like to make?	Presentation of information within the box in bulleted format would improve readability.
8	**Process Requirements**	
Q14	Do you support the proposal? ~~Yes/No~~/**With modification**	MA supports the proposed process for changing or removing a Boxed Warning with modification • As inclusion of a Boxed Warning is a risk mitigation activity and negotiated through sponsor negotiations with the TGA, precise instructions are required to guide the process and decision making for making changes or removal. • Decisions on changes to or removal of Boxed Warnings should be decisions under Section 60 of the Therapeutic Goods Act. • Timing of a TGA requested Boxed Warning should occur as early as possible, and no later than the Delegate's request for pre-ACM advice for major Category 1 applications. This then avoids delays to approval of the product/variation due to a more protracted post-ACM PI negotiation phase. Furthermore, the ACM also then has the opportunity to comment on the appropriateness of the Boxed Warning as well as the Sponsor accompanying comment on the proposal. • It should be clarified whether the TGA will not implement amendments to a Boxed Warning unilaterally. The sponsor should always have an opportunity to evaluate proposed amendments to existing Boxed Warnings before implementation.
Q15	Do you envisage any difficulties with the proposed process? **Yes**	The proposed process is vague and precise instructions on process and decision making are required. • The guidance has specific descriptions on the evidence which may lead to a Boxed Warning. There is much less guidance on the evidence required to remove a Boxed Warning. It appears it will be much easier for the TGA to require and implement a Boxed Warning than for the Sponsor to remove one.

Page	Item	Comments and Rationale
		• Without clear understanding on the requirements to apply for removing a Boxed Warning, it can lead to wasting the sponsor resources such as conducting trials, prepare applications and also the TGA resources to evaluate the applications which may have been successful and efficient if the requirements are defined in advance. • In absence of clear guideline on the requirement for removing a Boxed Warning, there is a potential that an active ingredient related effect can be removed for one brand based on a low quality evidence and not for the other brands or generic products.
Q16	Are there other modifications to the proposal you would like to make? **Yes**	• A uniform and transparent process should be adapted governing decisions to remove Boxed Warnings to ensure consistency across the industry It should be clear what type of evidence should be required to remove a Boxed Warning e.g Periodic Safety Update Reports (PSURs), what type of trials, use of comparator in the study. • The recent draft updates to the TGA guidance on RMPs do not describe any requirements to submit an updated RMP when introducing a Boxed Warning. A reference to the use of a Boxed Warning may be described in the routine risk minimisation activities section of the ASA. However, an update to this section alone, assuming that the risk profile of the drug described in the submitted RMP is unchanged, should not require a submission to the TGA in its own right. • The text that the Boxed Warning may be amended by the TGA based on evidence from reputable sources, should be amended as it is too vague. The evidence should be robust and should reflect the amended content proposed above for page 5 of the guidance document (see Q2 and Q3 above).
9	**Promotional Material**	
Q17	Which of the above options do you support? Option 1/**Option 2**/Other (please provide details)	• MA supports Option 2 which is aligned with the current Medicines Australia Code of Conduct requirements. An allowance for the Boxed Warning to appear as the first part of the minimum PI is also more practical considering the range of communication channels now available. • MA recommends the Guidance provides instruction on inclusion of Boxed Warning for products with multiple unrelated indications/uses, noting that the Boxed Warning may not be required to be included in materials that do not relate

Page	Item	Comments and Rationale
		to all indication/uses or the indication/use requiring significant caution.
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)?	MA supports keeping the current practices as outlined in the current Medicines Australia Code of Conduct Guidelines • There are some circumstances in which a minimum PI is not necessary and a link to the full PI can be provided ie. for electronic and audiovisual materials, internet and e-newsletters. In these instances, the Boxed Warning is provided at the end along with the PBS restrictions and a statement to review PI before prescribing. • The TGA refer to brand name reminders in the guidance. However, brand name reminders are no longer permissible under the MA Code. Clarification is required if the TGA are referring to "items containing small advertisements" (ie. desksets, calendars etc) where, due to space constraints, the minimum PI and PBS information appears elsewhere. • For completeness, the guidance should confirm that "Boxed Warnings are not required on non-promotional materials including those defined as Additional Risk Management Materials."
10	**Timelines and Implementation**	
Q19	Do you support the proposal? ~~Yes/No~~/**With modification**	MA supports the proposal for timelines and implementation with modification • If there will be changes impacting the PI, CMI and/or promotional material then there should be an appropriate phasing of implementation and there should be further consultation to develop the implementation parameters. • Boxed Warnings provide the most value in the early use of medicines following registration of the product or upon their introduction following a change in use of the product or new significant safety information. There is diminished value of retrofitting materials for existing products and indications. All documents for a specific medicine should be aligned with respect to the inclusion of a Boxed Warning.
Q20	Do you envisage any difficulties with the proposed prospective implementation?	• If Option 1 for promotional material is adopted and/or changes impacting PI and CMI are to be implemented, there will need to be a permissible amount of time for a company to update and implement changes to materials, particularly for hard copy materials. Changes cannot be implemented immediately upon the guidance being published.

Page	Item	Comments and Rationale
Q21	Are there other modifications or additions to the proposal you would like to make?	• Boxed Warnings should include clear actions to be taken to manage, avoid and/or mitigate risks/consequences. • Warnings based on animal data that do not have direct relevance to humans should not be included in Boxed Warnings. • If changes to existing materials are necessary, a grace period for implementation should apply. Materials currently have a lifecycle of 2 years.
	Other	
	Impact of proposed changes on industry • Likely benefits • Costs – financial and non-financial	• Likely benefits include clear direction on circumstances for Boxed Warnings, clear instructions for its appearance and references to it, and consistency in approach • If Option 1 for promotional material is adopted and/or changes impacting PI and CMI are to be implemented, then both financial and non-financial costs will be incurred to re-publish and/or re-print promotional materials, package inserts, upload revised documents to websites • Inconsistent implementation of guidance requirements between TGA Delegates may result in additional red tape for Sponsors and a lack of international harmonisation on perceived benefits/risks which can be confusing to healthcare professionals and patients. This has the potential to impact clinical prescribing decisions and consequently clinical outcomes.

References

1. Forbes N; Cooray M; Al-Dabbagh R; Yuan Y; Tse F; Liu LW; Xenodemetropoulos T. Domperidone prescribing practices exposed patients to cardiac risk despite a 'black box' warning: A Canadian tertiary care centre study. Canadian Journal of Gastroenterology & Hepatology. 2016; 2937678.

2. Moeller KE, Shireman TI, Generali J, Rigler S, Mayorga A. Pharmacy Students' Knowledge of Black Box Warnings. American Journal of Pharmaceutical Education. 2010; 74 (1) Article 5.

3. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA. Geographic Variation in the Response to FDA Boxed Warnings for Rosiglitazone. N Engl J Med. 2010;22:2081-2084.

4. Tong V, Raynor DK, Blalock SJ, Aslani P. Exploring consumer opinions on the presentation of side-effects information in Australian Consumer Medicine Information leaflets. Health Expectations, 19, pp.543–556.

5. Wagner AK , Chan KA, Dashevsky I , Raebel MA, Andrade SE, Lafata JE, Davis RL, Gurwitz JH, Soumerai SB, Platt R. FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full. Pharmacoepidemiol Drug Saf. 2006; 15 (6): 369-386.