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31 Aug 2018

Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
DUE DATE: 31 August 2018

Dear Sir/Madam

Boxed Warning Guidance

AbbVie Pty. Ltd. (AbbVie) would like to thank the Therapeutic Goods Administration (TGA) for the opportunity to review and comment on the consultation paper 'Boxed Warning Guidance'.

AbbVie supports the provision of a guidance paper on the topic Boxed Warnings. AbbVie has reviewed the questions proposed by TGA throughout the paper and provided comments in the below table.

To ensure that the utilisation of a Boxed Warning in the Product Information document as a risk mitigation measure is fully understood by prescribers, pharmacists, and consumers, AbbVie recommends that TGA undertake a comprehensive educational program to support the implementation of this guidance.

AbbVie are aligned with the industry submission from Medicines Australia's Regulatory Affairs Working Group (RAWG) and its Expert Advisory Group on Pharmacovigilance.

Should you have any queries regarding this submission please contact me by email at xxxxxxxxxxxxxxxxxxxxxxx.

Yours Sincerely

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Page \ Question Number	Question	Proposed Change	Rationale or Comment
Page 5; Q1, Q2, Q3	Required Evidence to support a boxed warning	Removal of the following phrases are proposed: • "where causality is not fully demonstrated" and, • "If a particular safety signal occurs for one medicine within a class, but not another."	AbbVie support the proposal ***with modification*** (c) • Given that the boxed warning is to convey serious risk, the causal relationship should be assessed, as suggested, as "reasonable possibility"; however, it should not be required "where causality is not fully demonstrated". Removal of the latter phrase is proposed i.e. "A boxed warning may also be required if the safety issue is of sufficient concern." • In addition, whilst it would appear reasonable to state that a boxed warning may be removed if further data becomes available that provides evidence against the causation, however, over time there may be situations where lack of available data may also support the removal of a boxed warning, particularly in cases, where the warning is based on indirect evidence or was assigned due to a proposed class effect. If the required evidence base is ultimately amended to ensure that causality must be established, then this is not an issue, however, if the proposed evidence base is retained, then this becomes more relevant. We suggest that the section "A boxed warning may be required : • On the basis of indirect evidence or an anticipated effect (e.g. class effect) • If a particular safety signal occurs for one medicine within a class, but not another" be deleted, based on the fact that causality has not been established and whilst it is appropriate to include these

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			warnings in the body of the PI, it is a low level of evidence to suggest it is a class effect when it is only an anticipated effect or occurs for one medicine but not another in a particular class. • Clarification required for the definition of "indirect evidence", in addition to examples.
Page 6; Q4, Q5, Q6	When a Boxed Warning is proposed	Removal of points proposed: • "There is markedly reduced effectiveness or evidence of net harm in certain patient population" and, • "In some circumstances Boxed Warnings may be based on evidence drawn from "off-label" populations ..."	AbbVie support the proposal ***with modification*** (c) • Markedly reduced efficacy or evidence of net harm is adequately covered by indications and contraindications in a PI. There are examples of this in targeted oncology medicines that involve assessment of tumours for genetic mutation. Prescribing to the "wrong" population is not in the best interest of the sponsor, as well as the patient. • Adding a boxed warning for off-label populations also seems unreasonable, given that prescribers have the ability to prescribe off-label if, in their clinical judgment, it is considered warranted. If there is a substantial risk, this can be addressed in contraindications, or warnings and precautions. Given this information is proposed to be carried over into the CMI, it is potentially alarming to patients to receive irrelevant black box warning information. • AbbVie recommends further clarifications and/or examples of

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			what constitutes a 'non-actionable reactions'.
Page 7; Q9, Q10	Boxed Warning and CMI		AbbVie support the proposal ***with modification*** (c) • Not all boxed warnings will be relevant to patients, given they are aimed at providing the prescriber with important safety information. They may address off-label indications and may be cause alarm to patient, who are using in line with approved indications. Whilst the proposed document states that the CMI statements should be aimed at the patient and need not be identical to the statement in the PI, it is not clear whether this provides the opportunity to omit certain black box warnings from a CMI, because they are not providing any useful information for a patient, or whether this means that black box warnings need to be reworded so they can be understood by patients. We support the former. Whilst we always aim at providing information in the CMI that is easily understood by patients, it's not clear what level of evidence will be required to substantiate that it can be understood or how TGA will determine that the requirement has been met.
Page 8; Q11, Q12, Q13	Format of the Boxed Warning in the PI		AbbVie support the proposal (a)

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Page 9; Q14, Q15, Q16	Process Requirements		AbbVie support the proposal (a) • We agree in principle that the evidence used to amend a black box warning should be from a reputable source, this is a different standard than is applied to the standard of evidence used to establish the back box warning in the first place (i.e. it can be a suspected class effect with no causality established). We recommend that TGA are consistent with respect to evidence required.
Page 10; Q17, Q18	Promotional material		Option 2 is adequate and aligns with the Medicines Australia Code of Conduct guidelines. Sponsors are sufficiently responsible in communicating the information, and providing the option of having the Boxed Warning included in full or referenced prominently, as per Option 2, is reasonable.
Page 10, Q19; Q20; Q21	Timelines and implementation		AbbVie support the proposal ***with modification*** (c) • AbbVie, agrees with the proposal that the guidance applies prospectively, based on new safety information (for existing products) No concerns about immediate implementation – other than if a boxed warning is due to a class effect, that all sponsors implement concurrently to avoid the impression that some products are 'safer ' than others. • Given that a boxed warning conveys serious risk information, it should be included for all sponsors' PI. The language in this section is a little

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			insipid and in favour of generics, viz "… some or all sponsors' PI …", and "… a Boxed warning may also become relevant to all other sponsors' PI". The wording in this section should be strengthened. • AbbVie recommends adding a reference to biosimilars and reference biological products similar to the proposed statement "This also applies to generic products that include a Boxed Warning in line with the brand leader product."