GSK and ViiV Comments on TGA Consultation: Boxed Warning Guidance (August 2018)

Overall Comment

GlaxoSmithKline (GSK) and ViiV Healthcare (ViiV) welcome the opportunity to comment on the TGA consultation to introduce a Boxed Warning guidance document.

In this document, GSK and ViiV collectively have provided view points for consideration on the proposed guidance. There is overall support for the introduction of a guidance and the proposed amendments to the current process, however there is still scope for further clarity and refinement.

General Comments

- GSK/ViiV support the introduction of a guidance document outlining the requirements and process for Boxed Warnings.
- Boxed Warnings have a place in highlighting the careful use of a medicines for certain patient populations, however their use should be carefully assessed on an individual basis taking into account the increased pharmacovigilance activities and monitoring now required. In order for Boxed Warnings to have the desired impact, they should only be used when the risks cannot be adequately addressed by the Contraindication or Special Warning and Precautions for use sections of the Product Information (PI) or by other risk minimisation activities such as Health Care Professional and patient educational programs.
- The introduction of materials with black triangles and potentially more Boxed Warnings needs to be managed carefully in the community, especially given the already sensitive opinion on earlier approvals, less evidence, safety issues etc. associated with the new evaluation pathways.

Response to Specific Questions

Required evidence to support a Boxed Warning

Q1: Do you support the proposal for evidence?
a) yes
b) no
c) with modification

Response:
With modification

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

Response:

- It should be clarified in what circumstance data from off-label use would be used by the TGA. As data from off-label use will not provide evidence related to the intended use of the medicine, it should only be used in exceptional circumstances.
- Further clarity on what "additional studies or independent sources" would be considered sufficiently robust by the TGA is needed. The evidence for a Boxed Warning needs to be as robust as the evidence used for all other sections of the PI.

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

Response:

- Addition of further details outlining the circumstances and criteria off-label data and independent data sources would be used.

When a Boxed Warning is proposed

Q4: Do you support the proposed circumstances?
a) yes
b) no
c) with modification

Response:
With modification

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

Response:

- The level of evidence and criteria for adding Boxed Warnings is somewhat vague. It will not help Sponsors understand when and why a boxed warning would be requested. It would be helpful for the TGA to base this on the criteria they have used for the current Boxed Warnings.

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

Response:

- The second bullet point regarding serious adverse reactions describes criteria very similar to that used to determine what is to be included in Special warnings and precautions for use section of the PI. Further information is required to differentiate these criteria.

Content of the Boxed Warning in the PI

Q7: Do you support the proposal?
a) yes
b) no
c) with modification

Response:
Yes

Q8: What changes would you propose?

Response:
No changes are proposed. GSK/ViiV support the boxed warning containing succinct warning statement only, which is in line with current practice.

Content and Format of the Boxed Warning in the CMI

Q9: Do you support the proposal?
a) yes
b) no
c) with modification

Response:
With modifications

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

Response:
- GSK/ViiV support inclusion of Boxed Warnings in the CMI. It will be necessary to include more information and context for patients within the boxed warning than what may be required for HCPs.
- Where possible, the information for patients should be "actionable" (e.g. stop the drug, or call your doctor if you experience x, y or z).

Format of the Boxed Warning in the PI

Q11: Do you support the proposal?
a) yes
b) no
c) with modification

Response:
Yes.

Q12: What changes would you propose?

Response:
No changes are proposed. GSK/ViiV support the guidance on the format of Boxed Warnings to ensure consistency across PIs and CMIs.

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

Response:
No modifications are proposed.

Process requirements

Q14: Do you support the proposal?
a) yes
b) no

c) with modification

Response:
With modification

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

Response:
- Additional information is required regarding the data requirements for the amendment or removal of a boxed warning. Specific guidance is given on the evidence requirements to add a boxed warning. A similar level of information should be provided for the amendment or removal of Boxed Warnings. Alternatively, a cross reference should be included between the two sections if the same evidence is required.

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

Response:
- Further information should be given on the timing of when a request for a boxed warning will be made during the evaluation of a Category 1 application. This should be made before or at the time of the Delegate request for advice to allow the AMC/ACV to consider the request and to avoid delays in approval due to lengthy post-ACM/ACV PI negotiations.

<u>Promotional material</u>

Q17: Which of the above options do you support?
a) Option 1
b) Option 2
c) Other (please provide details)

Response:
Option 1 with elements of 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)?

Response:
- When considering Option 1, further clarity is required on whether there would be a requirement for the boxed warning to appear at the beginning of the promotional material, as per Option 2.
- Whilst Option 2 in some way aligns to the requirements of MA (that being, "*for prescription products that have a boxed warning included in their Product Information, all promotional material must include the boxed warning or a prominent statement drawing attention to the boxed warning*"). However, there is no requirement for this to appear at the beginning of the material. In fact, the Boxed Warning appears with the minimum PI at the end of the promotional piece with the purpose of providing sufficient, relevant information to a healthcare professional in the context of viewing promotional material and advertisements. By appearing in connection with the minimum PI, there is context provided to the statement contained within the boxed warning.

- It should also be noted that there are some circumstances in which a minimum PI is not necessary and a link to the full PI can be provided instead. For example, for electronic and audio-visual 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 the PI before prescribing.
- The draft guidance refers to brand name reminders in the guidance. However, brand name reminders are no longer permissible under the MA Code. Clarity is needed on whether the guidance is in fact referring to "items containing small advertisements" (i.e. desksets, calendars etc) where, due to space constraints, the minimum PI and PBS information appears elsewhere.

Timelines and implementation

Q19: Do you support the proposal?
a) yes
b) no
c) with modification

Response:
Yes

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

Response:

- GSK/ViiV support the implementation of any changes to the current process and format prospectively rather than retrospectively. However, it would be helpful for the TGA to confirm that these changes will not be necessary when there are updates to a PI, CMI or promotional materials for products with existing Boxed Warnings.

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

Response:
No further modifications are proposed.

We thank the TGA for providing GSK/ViiV with the opportunity to participate in this consultation process.

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