

❖ When a safety concern should be elevated to a Boxed Warning

While the current, non-exhaustive list of scenarios provided in the draft guideline is a good compilation of circumstances under which a risk may deserve “highlighting”, this list also describes circumstances under which a risk would normally meet the threshold for inclusion in the SPECIAL WARNINGS AND PRECAUTIONS FOR USE section. Therefore, the list alone is inadequate to explain when a risk is sufficiently outstanding in its importance to qualify for a Boxed Warning.

For risk communication, such as in labelling, the prominence a risk deserves depends on both the characteristics of the risk (such as severity/seriousness, likelihood of occurrence, need for precautions or intervention) and other factors (such as magnitude of benefit, public health concerns, importance of consideration in individual benefit-risk decisions, expected likelihood that the risk or necessary precautions might be ignored).

The key criterion for deciding on the need to give a risk particular prominence at the boxed warnings level is the requirement for “drawing clear attention to the particular risk” (as currently stated under the 3rd bullet of the list of scenarios). Also, when describing circumstances that make a risk outstanding and in which a Boxed Warning may be indicated, the draft guidance uses the following phrases:

- “... so serious that it is essential that it be considered ...”
- “... information that is especially important to the prescriber ...”

BioMarin recommends that TGA present this aspect as the primary, overarching criterion for determining whether a risk deserves being elevated to a Boxed Warning. To emphasize the key criterion that determines outstanding importance and the need for particular prominence (i.e., presentation as a Boxed Warning), BioMarin also recommends modifying the draft guideline text as shown below. This modification will clarify the role of TGA in assessment and decision making.

TGA may require a Boxed Warning if TGA determines that awareness of the risk and the information provided are so important that using a Boxed Warning is essential for risk minimisation. A Boxed Warning may be appropriate in various situations. **Situations, in which TGA may determine that a Boxed Warnings is essential for risk minimisation, include:** ~~The following list of scenarios is not meant to be exhaustive:~~

❖ Promotional Material

BioMarin supports Option 2 with modifications. Option 2: *all promotional materials must include the Boxed Warning in full or contain a prominent reference to the Boxed Warning ~~at~~ in the beginning of material).*

We propose this modification to avoid inconsistency with other regions that do not require placement of the Boxed Warning at the “beginning” of material.

In summary, Boxed Warnings should be included in exceptional cases where the warning is particularly important. The causality should be determined based on thorough assessment by the sponsor and ongoing risk assessment which is discussed between the TGA and the sponsor.

We thank TGA for this opportunity to comment on this important guidance and we look forward to working closely with TGA to develop a robust guidance for Boxed Warnings.

If you have any questions, please don't hesitate to contact me on xxxxxxxxxxxxxxxx.

Yours sincerely

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