Safety issues

Significant safety issues

A significant safety issue (SSI) is a safety issue relating to your ARTG-listed or registered medicine that requires the **urgent** attention of the TGA as it is likely to warrant prompt regulatory action. It is significant because of the seriousness and potential major impact to the benefit-risk balance of the medicine and public health.

Examples of SSIs include:

- the following major safety-related actions by other overseas regulators:
  - the withdrawal or suspension of the medicine's availability
  - the addition of a boxed warning, modification or removal of an indication (for safety reasons), or addition of a contraindication to the product information or label.
- major safety findings from a newly completed non-clinical study, post-registration study or clinical trial that are likely to impact the benefit-risk balance of the medicine e.g. an unexpected increase in the rate of fatal or life-threatening adverse events
- major safety issues identified through spontaneous reporting or published literature, which may lead to the addition of a contraindication, restriction of the use of a medicine, or its withdrawal from the market.

Professional judgement should be used to determine whether a safety issue is significant. Each safety issue should be assessed on a case-by-case basis and evaluated to determine whether it has a major impact on the medicine's benefit-risk balance and/or implications for public health.

Significant safety issues **MUST** be reported as soon as possible and no later than 72 hours from awareness. The clock for reporting (Day 0) begins as soon as personnel of your Australian affiliate (including any third parties, vendors or partners that have been delegated pharmacovigilance responsibilities):

- become aware of the major safety-related actions of another regulator, or
- establish that a safety issue from any source meets the definition of an SSI.

We recognise that safety information may be received and processed by your global counterparts before it is disseminated to the local affiliate.

We expect you to have clearly documented internal procedures in place to ensure expedited communication of SSIs from global personnel to your relevant Australian personnel for reporting. Your procedures should ensure that SSIs will be communicated from global to Australian personnel in no more than 3 calendar days, and more rapidly for the most serious safety issues. You **MUST** keep records of communications including dates when global and local personnel were notified and reasons for any delays.

Where you have contractual arrangements with a third party (external) person, other sponsors or external organisations, your pharmacovigilance contract or agreement should outline roles, responsibilities and timelines to ensure you can comply with your reporting obligations for safety issues.

The reporting clock restarts when you receive additional clinical or medically relevant information related to a previously reported SSI.

We use the information you report to take appropriate action. This may include providing further safety information to the public, requesting updates to product information documents, imposing additional risk management interventions or pharmacovigilance activities, or (rarely) removing a medicine from the market.

Other safety issues

Other safety issues (OSIs) are safety issues that require action by the TGA but do not need to be actioned urgently. These issues are unlikely to alter the benefit-risk balance of the medicine.

Examples of OSIs include:

- internally identified signals that have undergone a signal assessment and identified a new or changed risk
- safety-related changes by overseas regulators to the product information documents or labels (that do not meet the definition of an SSI)
- safety issues due to incorrect or out-of-date information in the product information document
- safety issues related to established use outside the approved indication or intended use (off-label use)
- changes in the severity or frequency of a known serious adverse reaction
- identification of clinically significant risk factors for the development of a known adverse reaction.

Other safety issues **MUST** be reported to the TGA within 30 calendar days of establishing that a safety issue exists. Day 0 is the day that your internal signal assessment is completed.

A safety issue leading to regulatory action by another overseas regulator is reportable irrespective of whether you agree with the recommendations and conclusions of the regulator.

If you determine after appropriate assessment that a safety issue does not require reporting, you should document a justification for this decision. We may ask you to provide this documentation at any time.

Information that does not need to be reported

The TGA does not need to be notified of the following types of information:

- An overseas regulator's request for further information or data from the sponsor for assessment (e.g. an EMA Pharmacovigilance Risk Assessment Committee request for a cumulative review of the available evidence for a safety issue)
- Notification that an overseas regulator has identified a new safety issue and will be undertaking an evaluation (e.g. the US Food and Drug Administration are evaluating a Newly Identified Safety Signal)
- A signal evaluation that has been conducted by an overseas regulator where no regulatory action is recommended
- An internally identified signal that is subsequently refuted.

If in doubt, contact the TGA for advice.

A decision tree outlining the SSI and OSI notification process is included in this document as Appendix A.

How to report a safety issue

All safety issues should be reported to the TGA by emailing a completed *safety issue reporting form* to the Pharmacovigilance Branch Signal Investigation Coordinator (si.coordinator@health.gov.au).

To assist us in evaluating the safety issue you **MUST** provide us with any additional information we request.

Where a safety issue will result in urgent changes to the Australian Product Information or you are liaising with a Clinical Delegate regarding the issue, please copy the Signal Investigation Coordinator in your communications to the applicable TGA Clinical Delegate.

Appendix A – Safety issue reporting decision tree