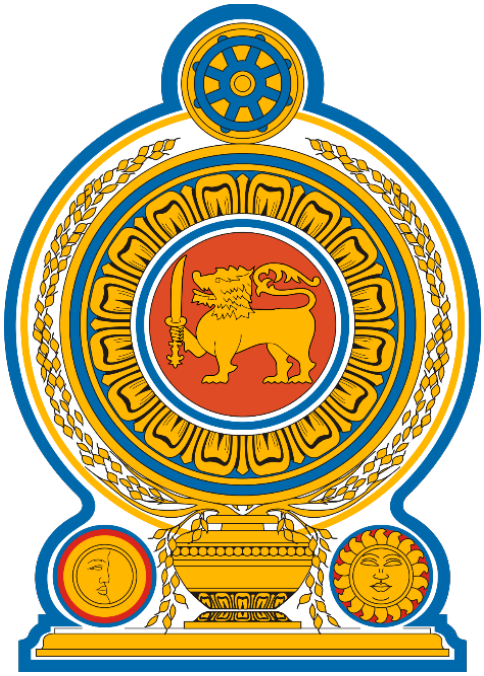

Guideline on Risk Management System

NATIONAL MEDICINES REGULATORY AUTHORITY
NORRIS CANAL ROAD, COLOMBO 10, SRI LANKA

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Risk management systems

1. Principles of Risk management

A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Generally, a medicinal product will be associated with adverse reactions. However, not all adverse reactions and risks will have been identified at the time when an initial marketing authorization is granted and some will only be discovered and characterized in the post-authorization phase.

The overall aim of risk management is to ensure that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin throughout a medicinal product's life cycle. The risk management plan (RMP) is a detailed description of a risk management system. Accordingly, the RMP is a dynamic document that should be updated throughout the life cycle of the product(s) as new knowledge and understanding of the products' safety profile evolve over time.

To this end, the RMP contains:

1. '**safety specification':** the identification or characterization of the safety profile of the medicinal product, with emphasis on safety concerns:
   - important identified risk
   - important potential risks
   - missing information, and also
   - on which safety concerns need to be managed proactively or further studied;
2. **'pharmacovigilance plan':** the planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions;
3. **'risk minimization plan':** the planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities.

1.1. Safety concerns

The RMP should focus on those risks that are relevant for the risk management activities for the authorized medicinal product.

Safety concerns

An important identified risk, important potential risk or missing information.

Important identified risks

From the identified risks of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is sufficient scientific evidence that they are caused by the medicinal product.

Reports of adverse reactions may be derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature. They may be linked to situations such as off label use, medication errors or drug interactions.

Not all reported adverse reactions are necessarily considered a relevant risk of the product in a given therapeutic context. The RMP should focus on the **important identified risks** that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant:

- Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk);
- Risk minimization activities: product information advising on specific clinical actions to be taken to minimize the risk, or additional risk minimization activities.

Important potential risks

From the potential risks of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.

The **important potential risks** to be included in the RMP are those important potential risks that, when further characterized and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Where there is a scientific rationale that an adverse clinical outcome might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product, the adverse reaction should be considered a potential risk, and if deemed important, should be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

Missing Information

Missing information relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilization (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

1.2. Types of activities in RMP

Pharmacovigilance activities are interventions designed to identify, characterize safety concerns in the product's safety specification or to assess of the effectiveness of risk minimization measure.

Risk minimizations activities are interventions designed to prevent or minimize safety concerns in the product's safety specification.

Both pharmacovigilance activities and risk minimization activities may be classified as:

- 'routine' (which apply to all products) or
- 'additional' (for some risks considered when routine activities will not be sufficient).

Examples of routine and additional activities

	Routine	Additional
Pharmacovigilance activities	• collection and handling of ICSRs, • PSURs, • signal management, • literature monitoring • Specific adverse reaction follow-up questionnaires • enhanced passive surveillance system	• Clinical trials • Non-clinical studies • Post-authorization safety studies • Patient registries
Risk minimization activities	• the summary of product characteristics; • the labelling (e.g. on inner and outer carton);	• Educational materials for health professionals and/or patient • Controlled access programs

	• the package leaflet; • the pack size(s); • the legal status of the product.	• Pregnancy prevention programs • Direct healthcare professional communication

1.3. Evaluation of the effectiveness of risk minimization activities

When the RMP is updated, the risk minimization plan should include a discussion of the impact of additional risk minimization activities.

To evaluate the effectiveness of additional risk minimization measures two categories of indicators should be considered:

- process indicators;
- outcome indicators

If a particular risk minimization strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then consideration should be given to alternative activities. The MAH should comment in the RMP on whether additional or different risk minimization activities are needed for each safety concern or whether in their view the (additional) risk minimization measures may be removed (e.g. when risk minimization measures have become part of standard clinical practice).

If a study to evaluate the effectiveness of risk minimization activities is conducted, the study should be included in the pharmacovigilance plan, part III of the RMP.

2. Content of the RMP

The RMP consists of seven parts as listed below; certain parts specifically the Safety specification are subdivided into modules so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan.

Part I: Product(s) overview
Part II: Safety specification
Module SI: Epidemiology of the indication(s) and target population(s)
Module SII: Non-clinical part of the safety specification
Module SIII: Clinical trial exposure
Module SIV: Populations not studied in clinical trials

Module SV: Post-authorization experience

Module SVI: Additional requirements for safety specification not discussed in ICH-E2E (e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error)

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

Part III: Pharmacovigilance plan

Part IV: Plans for post-authorization efficacy studies

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)

Part VI: Summary of the risk management plan

Part VII: Annexes

For detailed description of each part of the RMP the MAH and its local representative should refer EMA GVP Module V – Risk management systems.

2.1. Acceptable Risk Management Plan Format

Generally, in Sri Lanka, the EU RMP template is the acceptable approach to fulfilling requests by NMRA for RMPs:

- **Integrated format:** a full EU RMP template (integrated format) is suitable for the originator medicinal products, however
- **Abridged format:** an **abridged format** of the EU RMP template can be used in generic products and some situations as described below.

Summary of RMP requirements and abridged format of RMP for different product types

Product	Part I	Part II								Part III	Part IV	Part V	Part VI
		SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
Originator	√	√	√	√	√	√	√	√	√	√	√	√	√
Generic	√					√	‡	‡	√	√	*	∫	√
Fixed combination – new active substance	√	∓	∓	∓	∓	∓	∓	√	√	√	√	√	√
Fixed combination – no new active substance	√		†	†		√	‡	‡	√	√	*	∫	√
Biosimilar	√		√	√	√	√	√	√	√	√	√	√	√

√ = applicable/relevant

‡ = relevant only if "originator" product does not have an RMP and its safety profile is not published on CMDh website

* = relevant only when a PAES was imposed by NMRA

∫ = statement of alignment of safety information in PI is sufficient

† = requirements based on risk proportionality principle, addressing new data generated or differences with the "originator" product
Ŧ = focus on the new active substance

2.1.1. RMPs for generic medicinal product:

For generic medicinal products an abridged format of the RMP can be used as highlighted in the table above. Furthermore, the following should be taken into consideration

Safety specification

- Align the summary of safety concerns for the generic with that of the originator, by referring to sources such as the European Public Assessment Report (EPAR) or the list of safety concerns per approved RMP of active substances per product, published by the "Coordination Group for Mutual recognition and Decentralized Procedures- Human" (CMDh)
- Consider whether there are any safety concerns specific to the generic product, for example:
  - if introduction of a generic in a different administration device could increase the risk of medication error with a significant impact on public health or for the individual (for example, lack of efficacy for a life-threatening condition or an increased risk of adverse effects)
  - if introduction of a generic without presentations suitable for use by particular patient populations, such as children or people with particular conditions, may require additional education of health professionals
  - Risks associated with a new excipient

Pharmacovigilance plan

If there are specific adverse-event follow-up forms implemented for the originator, these should also be implemented for the generic.

Risk minimization plan

- Generally, a full part V is required for the generic product if the originator product has additional risk minimization activities
- However, the need for additional risk minimization activities to be undertaken for generic medicines can be evaluated, taking into account factors such as:

- the nature and purpose of the additional risk minimization activities required for the originator
- whether the additional risk minimization activities required for the originator are ongoing
- whether the relevant safety concerns are adequately mitigated by routine clinical practice
- any safety concerns specific to the generic need to be addressed by additional risk minimization activities

- Additional risk minimization materials for generics should cover the same key safety messages as those for the originator, and any safety concerns specific to the generic.

2.1.2. RMPs for fixed combination medicinal products:

- If the combination contains a new active substance: A full (integrated) RMP should be submitted. RMP modules SI-SVI should focus on the new active substance.
- If the combination does not contain a new active substance: The RMP should follow the elements for a generic product (abridged). For the purpose of establishing the elements of RMP part II, "the originator product" should be read as "any/all authorized products containing the same active substances included in the new product".
- In addition, new data generated with the fixed combination should be provided in modules SII and SIII.

2.1.3. RMPs for Biological products:

- RMPs for biological products should follow the EU RMP in the integrated format.
- For biosimilar product, only RMP module SII can be removed
- The RMP elements and consideration described in EU GVP guideline Product-Specific Considerations II: Biological medicinal products should be followed.

2.1.4. For Multinational, international companies and importers the following conditions apply:

- They should submit the EU RMP (in integrated or abridged format as applicable to the product type) accompanied by **Sri Lanka- Specific Annex (SSA)** to highlight the differences between the plan for the EU RMP and Sri Lanka
- The submitted EU RMP must be the most up-to-date version relevant to the submission

- If the EU RMP is under consideration by the EMA it will be acceptable for submission if there is no approved version of the EU RMP.
- If no EU RMP exists, then MAH may submit an alternative RMP, such as a global or core RMP provided that it must:
  - cover all of the modules of the EU RMP,
  - be presented in the current EU RMP format, and
  - be accompanied by the Sri Lanka- Specific Annex (SSA)

2.1.4.1. Sri Lanka Specific Annex (SSA)

The purpose of the "SSA" is:

- to highlight to what extent the risk management activities proposed to be implemented nationally adhere to the globally implemented plan and;
- to provide justification for any difference (apart from what implemented in EU) whenever exist including the needed national tailoring if any.
- In addition, it should include an assessment whether there are any additional national -specific risks or not, describing the may be added activities to manage those additional risks.
- It provides good evidence that the LSR has clear understanding and commitment about the activities that will be implemented on the national level and how they will be implemented.

2.1.5. For national MAHs the following conditions apply:

They should submit Sri Lanka RMP in adherence to the acceptable EU RMP template whether integrated or abridged format as applicable to the product type.

3. Submission of the RMP

3.1. Application types in which RMP can be submitted

Initial RMP or an update RMP, as applicable, may need to be submitted at any time during a product's lifecycle and in different types of applications including: initial marketing authorization application, variation, renewal, standalone RMP, or other post authorization procedures, as applicable (e.g. with a submission of final study results impacting the RMP or with a PBRER for medicinal product when the changes to the RMP are a direct result of data presented in the PBRER, with the assessment of Signal or emerging safety issue if resulting in change of the list of safety concerns or activities of the RMP).

3.2. When RMPs are required

a) Initial marketing authorization application; RMP should be submitted as part of application for:

- New medicinal product (New Chemical Entity)
- All biological products including biosimilars
- Originator medicinal product with safety concern has been identified for which additional risk minimization activities are being conducted in reference countries
- Any medicinal product that is to be re- introduced to the market after being previously withdrawn due to a serious safety issue
- Generic medicinal product in the following situations:
  - there is an RMP for the reference/ originator product with safety concern has been identified for which additional risk minimization activities are being conducted
  - there is no RMP for the reference/ originator product but there are safety concerns (e.g. teratogenicity) with the substance that have required additional risk minimization or additional pharmacovigilance activities (examples but is not limited to, thalidomide, leflunomide, clozapine, lenalidomide and isotretinoin and derivatives of these products
  - changes compared with the reference/ originator medicinal product which suggest different/ new safety concerns such as, but not limited to, medication error (for example, different preparation instructions) or off-label use (for example, restricted indications)
  - Generic product of new Chemical Entity
- New fixed combinations of active substances will require an RMP when (Originator or generic products):
  - one of the active substances is a new chemical entity
  - one or more of the active substances requires additional risk minimization
  - the indication of the combination differs from the indications of the individual active substances
  - if the combination leads to a new safety concern, or if there are new safety concerns for any of the individual active substances.

b) Application involving a significant change to an existing marketing authorization; an RMP or RMP update should be submitted with:

- new dosage form;
- new route of administration;
- new manufacturing process of a biotechnologically-derived product;
- other significant change in indication;

  A significant change in indication is a change of authorized indication(s) of a medicinal product where the new treatment target population differs materially from the one for which the medicinal product was previously authorized. This includes (but is not limited to): a new disease area, a new age group (e.g. paediatric indication) or a move from severe disease to a less severely affected population. It may also include a move from 2nd line or other therapy or for an oncology product a change to the concomitant medication specified in the indication.

c) Renewal of the marketing authorization;

- RMP update should be submitted as part of this application if the product has an existing RMP, this is an important milestone where the MAH should review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimization activities and update the RMP in accordance.
- initial RMP should be submitted for products meeting the criteria stated under points a), d) and e) of this title

d) **At the request of the NMRA (at authorization, renewal and post-authorization**) when there is a concern about a risk affecting the risk-benefit balance or require additional risk minimization or additional pharmacovigilance activities. RMPs can also be requested by NMRA as part of an ongoing review or other situations in order to support informed regulatory decision for medicinal products.

e) **On the initiative of MAH (at authorization, renewal and post-authorization)** when they identify a safety concern with a medicinal product at any stage of its life cycle and which require additional risk minimization or additional pharmacovigilance activities.

f) **For already authorized medicinal products** before this guideline became into effect and where no previous RMP exists; RMP should be submitted for originator or generic products where the reference/ originator product has an RMP with additional risk minimization activities

3.3. Update of previously acceptable RMP

The MAH should consider the need to update the RMP and, as appropriate, review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimization activities when (for example but not limited to):

- preparing a PBRER
- an emerging safety issue has been identified which might constitute a safety concern
- signal has been identified which might constitute a safety concern
- release of final study report with results
- preparing for renewal of marketing authorization
- preparing for variation
- measuring the effectiveness of the risk minimization measure

The MAH should submit an RMP update at any time when there is:

- a change in the list of the safety concerns, or
- a new or a significant change in the existing additional pharmacovigilance or additional risk minimization activities e.g. removing such activities from the RMP, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials.

Unless requested otherwise, a track-changes RMP document should be included with every RMP update, showing changes introduced in the latest update (as applicable), as well as compared with the "current" approved version of the RMP.

3.4. Consideration for submission timelines

When RMP submission is requested by the NMRA the timeline for submission of RMPs once requested by NMRA is 30 calendar days unless otherwise is stated in the request. When RMP is submitted in the context of other procedures; submission timelines of these procedures will apply.

3.5. Submission of educational materials

The following should be submitted to the NMRA:

- a cover letter including the following information:

- the contact details of the MAH and, if applicable, another organization to which it has subcontracted the submission (at least names and e-mail addresses);
- the regulatory procedure which has led to the need of the educational material(s) with supportive documents (e.g. NMRA decision/ request, approved RMP, assessment report identifying the need for this additional risk minimization measure "aRMM");
- a detailed implementation plan for the educational material with the following information:
    - target population(s);
    - dissemination method (e.g. paper, e-mail, via social media, learned societies and/or patient associations, publication on websites, other digital methods);
    - time point when dissemination is anticipated to start and frequency of further disseminations;
    - estimated date of launch or date of start of the marketing of the product (in the case of a new marketing authorization);

- draft educational material as documents in a common open text-processing electronic format of the proposed materials in language(s) required by NMRA;
- the intended layout and, where applicable, images and graphic presentations of the information (e.g. pictures, charts, diagrams, video).

When changes of the risk and/or the need for aRMM have been identified and changes in the key elements and/or in the content of the educational material(s) have been agreed with the NMRA, the MAH should submit to the NMRA revised proposals of the educational material after changes for assessment and approval. In the revised educational material, the changes should be highlighted against to the materials previously approved by NMRA.

4. Responsibilities of the MAH

Marketing authorization applicants are encouraged to plan from very early on in a product's life cycle how they will further characterize and minimize the risks associated with the product in the post-authorization phase.

In relation to risk management of its medicinal products, MAH and its local representative are responsible for:

- Having an appropriate risk management system in place;
- Design and submitting the RMP to the NMRA

- Ensuring that the knowledge and understanding on the product's safety profile, following its use in clinical practice, are critically reviewed. The MAH should monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products, and update the risk management system and the RMP accordingly.
- Consider the required different specialists and departments within and/or outside company upon producing a RMP
  - safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts;
  - pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them.
  - The design of risk minimization activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals;
- Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the MAH who should ensure oversight by someone with the appropriate scientific background within the company. Since a RMP is primarily a pharmacovigilance document, ideally the production of it should be managed by a qualified personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure.
- The MAH should implement measures adopted in the RMP after agreement with the NMRA.
- The MAH should provide information regarding the status of implementation of additional risk minimization measures as agreed with the NMRA and keep them informed of any changes, challenges or issues encountered in the implementation. Any relevant changes to the implementation of the tools should be agreed with the NMRA before implementation.
- For generic products the MAH should develop risk minimization in line with the scope, content, and format of the tools used for the reference/originator medicinal product. Scheduling and planning of interventions should be carefully coordinated in order to minimize the burden on the healthcare systems.
- The MAH shall monitor the outcome of risk minimization measures which are contained in the RMP and evaluate their effectiveness.

- The MAH should report the findings of the effectiveness evaluation when updating the RMP and in the PBRER.

For information about the principles of risk management, different types of activities Methods for effectiveness evaluation, the content of risk management plans and guidance on guidance on educational materials refer to:

- *EMA Guideline on good pharmacovigilance practices (GVP) Module V — Risk management systems*
- *EMA Guideline on good pharmacovigilance practices (GVP) Module XVI — Risk minimization measures: selection of tools and effectiveness indicators*
- *EMA Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum I – Educational materials*
- *EMA Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation*
- *EMA Guidance on the format of the risk management plan (RMP) in the EU — in integrated format*
- The *EMA GVP Parts on Product- or Population-Specific Considerations* should be consulted as applicable when preparing RMPs

5. Appendix: Risk Management Plan – Sri Lanka Specific Annex (SSA)

Applicable for Multinational, international companies and importers. They should submit the EU RMP in integrated format (for originator) or in abridged format (for generics). This EU RMP should be accompanied by Sri Lanka-Specific Annex (SSA) to highlight the differences between the plan for the EU RMP and Sri Lanka

I. Product Overview

Active ingredient(s) (INN):	
Pharmaco-therapeutic group (ATC Code)	
Manufacturer name:	
Local representative name:	
Product name(s):	
Brief description of the product (chemical class, mode of action, composition)	
Indication(s)	Current: *For initial marketing authorization applications, this section refers to the indication proposed by the applicant.* *For post-authorization procedures, it refers to the indication that is currently approved.* *With reference to the indication the EU/ reference country*
	Proposed (if applicable): *For post-authorization procedures, e.g. if the SAA is submitted with an extension/restriction of indication.* *With reference to the indication the EU/ reference country*
Dosage	Current
	Proposed
Pharmaceutical form(s) and strengths	Current
	Proposed
Is/will the product be subject to additional monitoring in the EU?	Yes/No

SSA version number:	
SSA version date:	
Referenced EU RMP version * and (date, data lock point)	

*Can be changed to 'core' or 'global' RMP if no EU-RMP is available

Local Safety Responsible (LSR) name ……..

LSR signature……

Contact person for this SSA……

E-mail address or telephone number of contact person

……

History of RMPs submitted in Sri Lanka

In this section, provide a tabulated history of EU RMP and SSA versions previously submitted for evaluation in Sri Lanka, with a summary of changes between versions. An example table format is shown below.

Table 1: History of RMPs/ SSA submitted in Sri Lanka (example)

EU RMP version	SSA version	Date submitted	Procedure or Update	Major changes to the SSA/Eu RMP from previous version

II. Safety specification

a. Summary table of Safety concerns listed in the EU RMP

Summary of safety concerns	
Important identified risks	• < > List
Important potential risks	• < > List
Missing information	• < > List

b. Safety concerns specific to Sri Lanka

Include details of any safety concerns for Sri Lanka that are additional to those proposed in the EU-RMP. This should include:

- *why the additional safety concern is included in the SSA (e.g. NMRA requirement, concern is specific to the Sri Lanka population)*
- *a detailed description of the safety concern (should be described in the same detail as used in the SVII.3 of the EU RMP (Rev 2), as shown below:*

< important identified/potential risk specific to Sri Lanka **>**

Potential mechanisms
Evidence source(s) and strength of evidence
Characterization of the risk
Risk factors and risk groups
Preventability
Impact on the risk-benefit balance of the product
Public health impact

< missing information specific to Sri Lanka **>**

Evidence source
Population in need of further characterization or Anticipated risk/consequence of the missing information

c. Proposed changes to Sri Lanka -specific safety concerns

This section can be used to request or record changes to Sri Lanka-specific safety concerns. If used, the section should follow the requirements for SVII.2 of the EU RMP (Rev 2):

<<Risk 1> is a new <important identified risk> <important potential risk> <missing information>>

<<Risk 2> previously classified as *<important identified risk> <important potential risk> <missing information>* is to be reclassified as *<important identified risk> <important potential risk> <missing information>* or *<is removed from the list of safety concerns>>*

Reasons for the reclassification or removal from the list of safety concerns:

<Changes in the level of scientific evidence for the causal association or risk-benefit impact >

For new proposals from the MAH/local representative, discuss briefly the level of scientific evidence that has led to this re-classification/removal.

III. Pharmacovigilance plan

a. Activities included in the EU RMP

In the following table; state clearly and justify any differences between routine and additional Pharmacovigilance activities described in the EU RMP and those proposed for Sri Lanka. Add rows as needed.

Details relevant to the differences in implementation of the activities in Sri Lanka compared to EU should be provided below the table as applicable

Describe by activity and not by safety concern (The reason for this is that one proposed activity (e.g. a prospective safety cohort study) could address more than one of the safety concerns.)

Activities as stated in the referenced EU RMP	Safety Concern(s)	Proposed for Sri Lanka?	Highlight differences if any (even minor difference)	Difference Justification

	addressed	*(Yes, No, Yes with differences)*	*(relevant details to be provided below the table)*	
Routine pharmacovigilance activities, beyond adverse reaction reporting and signal detection				
Additional Pharmacovigilance activities				

b. Sri Lanka -specific pharmacovigilance activities

This section should:

- *indicate whether there are routine (beyond adverse reaction reporting and signal detection) &/or additional pharmacovigilance activities for each Sri Lanka-specific safety concern,*
- *provide the detail of any Sri Lanka -specific pharmacovigilance activities addressing Sri Lanka-specific safety concerns, or*
- *provide the detail of any Sri Lanka -specific pharmacovigilance activities addressing safety concerns listed in the EU RMP but the activity is needed as "add-on" to those implemented in EU (e.g. national requirement)*

If there are no such specific pharmacovigilance activities, then this can be simply stated.

1. Sri Lanka -specific Routine pharmacovigilance activities

Provide a brief summary or list of routine pharmacovigilance activities, beyond adverse reaction reporting and signal detection, that will be implemented as Sri Lanka specific, if any, such as:

Specific adverse reaction follow-up questionnaires for <safety concerns>:

Provide the purpose and a description of the materials used when specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest are required.

***Describe by type of activity and not by safety concern**. The forms should be provided in Annex 1 of the SSA.*

Other forms of routine pharmacovigilance activities for <safety concerns>:

*This includes the description of following activities including objectives and milestones, e.g. enhanced passive surveillance high level description, observed versus expected analyses, cumulative reviews of adverse events of interest. **Describe by activity and not by safety concern**.*

2. Sri Lanka -specific Additional pharmacovigilance activities

For any additional pharmacovigilance activity that is Sri Lanka specific and is not described in the EU RMP, complete the following table, and provide the protocol in Annex 2 of the SSA, as shown below:

Study *(study short name, and title)* **Status** *(planned/on-going)*	**Summary of objectives**	**Study design**	**Study population**	**Safety concerns addressed** *(list)*	**Milestones** *(required by regulators)*	**Due dates** *(in DD/MM/YYYY format)*
LE observational cohort safety study (study LE123) *Planned*	*To evaluate over a minimum of 1 year the incidence of all-cause mortality and adverse events of special interest in patients with lupus erythematosus.*			*- serious infections (including non-serious and serious opportunistic infections and PML)* *- malignancies (including non-melanoma skin cancer)* *- serious infusion* *- hypersensitivity reactions* *- serious psychiatric events (mood disorders, anxiety and suicide).*	*Protocol submission*	*31/01/2019*
					Final report	*31/12/2018*
Post-marketing multi-centre registry study – REGAR02 *On-going*	*To investigate the association between the <product> induced QTc prolongation and possible predictive factors, and estimate the incidence of treatment-emergent adverse events of special interest.* *The study will also monitor the patterns of drug utilization for <product>.*			*Cardiac risk*	*Annual update*	*Progress reports on enrolment and intermediate analysis results will be provided yearly.*
					Final report	*31/03/2020*

IV. Risk Minimization Plan (including evaluation of the effectiveness of risk minimization activities)

a. Activities included in the EU RMP

Generally, it is required that all the risk minimization activities implemented in the EU/for originator product to be implemented in Sri Lanka as well, including the measurement of their effectiveness.

1. Routine risk minimization measures relevant to package insert

In the following table; describe the routine risk minimization measures relevant to package insert used for each safety concern. Identify and justify differences between the statements in the EU SmPC and PL versus national ones.

***Describe by safety concern**. Add rows as needed.*

Safety Concern	**Routine risk minimization activities in the EU SmPC & Patient leaflet**	**Differences between EU and Sri Lanka SmPC & Patient leaflet**	**Difference Justification**
Important identified risks			
Risk 1	In SmPC:		
	In patient leaflet:		
Risk 2	In SmPC:		
	In patient leaflet:		

Important potential risks			
Risk 1	In SmPC:		
	In patient leaflet:		
Risk 2	In SmPC:		
	In patient leaflet:		
Missing information			
Missing info 1	In SmPC:		
	In patient leaflet:		
Missing info 1	In SmPC:		
	In patient leaflet:		

2. Other routine and the additional risk minimization measures

In the following table; state clearly and justify any differences between routine and additional risk minimization activities described in the EU RMP and those proposed for Sri Lanka. Add rows as needed.

Details relevant to the differences in implementation of the activities in Sri Lanka compared to EU should be provided below the table as applicable

Describe by activity and not by safety concern (as one proposed activity could address more than one of the safety concerns).

Activities as stated in the referenced EU RMP	Safety Concern(s) addressed	Proposed for Sri Lanka? *(Yes, No, Yes with differences)*	Highlight differences if any (even minor difference) *(relevant details to be provided below the table)*	Difference Justification
Routine risk minimization measures, other than product information (e.g. Pack size, legal status)				
Additional risk minimization measures				

b. Sri Lanka -specific risk minimization measures

This section should:

- *indicate whether there are routine &/or additional risk minimization measures for each Sri Lanka-specific safety concern,*
- *provide the detail of any Sri Lanka -specific risk minimization measures addressing Sri Lanka-specific safety concerns, or*
- *provide the detail of any Sri Lanka -specific risk minimization measures addressing safety concerns listed in the EU RMP but the activity is needed as "add-on" to those implemented in EU (e.g. national requirement)*

If there are no such specific pharmacovigilance activities, then this can be simply stated.

For each Sri Lanka -specific additional risk minimization measures describe the following:

Objectives:

Include objectives including a list of risks addressed.

Rationale for the additional risk minimisation activity:

Include justification on why the particular additional risk minimization is considered needed.

Target audience and planned distribution path:

Include very brief summary of planned communication plan/ implementation methods with timeframes.

Provide copies of draft Sri Lanka educational materials in Annex 3. Materials should be provided with content and intended layout, including images and graphic presentations of information. For digital additional risk minimisation tools, provide content and images of the on- screen layout of the information, and/or the login details or access codes to enable the NMRA to evaluate the safety content in the format in which it is provided to the end user.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Describe the evaluation of each additional risk minimization activity to be conducted in Sri Lanka, including:

• how and when each activity will be evaluated

• how and when evaluation results will be reported to the NMRA

c. <Removal of additional risk minimisation activities>

<Rationale for the removal:>

Include justification when an additional risk minimization activity is proposed to be removed from the SSA.

Annexes

ANNEX 1. Follow-up forms to be implemented in Sri Lanka

ANNEX 2. Study protocols for planned pharmacovigilance studies in Sri Lanka

ANNEX 3. Additional risk minimization materials

Include draft versions for new submissions.
Include the key message(s) for additional risk minimization materials if key messages are not included in the EU RMP.
Include protocols for any studies to assess the effectiveness of additional risk minimization activities (if not attached to the EU RMP).

ANNEX 4. References