RMP assessment report sub-template for type II variations and PSURs

In case of RMP submission in a type II variation or a PSUR, please copy-paste the following section into the variation assessment report template. Only the relevant sub-headings (i.e. the ones for RMP sections being updated) should be used.

1. Risk management plan

Please copy from the below full structure of the RMP only the sections amended with the variation/PSUR into the variation/PSUR assessment report.

* 1. Safety Specification

*Epidemiology of the indications and target population*

*Clinical trial exposure*

*Populations not studied in clinical trials*

Comment on the relevance of the clinical trial population to the intended target population (inclusions, exclusions, limited numbers, trial setting, use in special populations). Comment on implications of scarce or missing information in relation to use in the target population.

*Post-authorisation experience*

Comment on any regulatory action for safety reasons. Comment on any post-authorisation use in populations with no or limited exposure during clinical trials. Comment on any off-label use unless covered immediately below.

*Additional EU requirements for the safety specification*

Potential for harm from overdose

This is especially important for medicines used by patients with psychiatric disorders or a medicine with a narrow therapeutic margin. Serious adverse events related to overdose should be reflected in the RMP.

Comment on the MAH’s text in the RMP on the potential for overdose. The information in this RMP section should be consistent with information to be included in section 4.9 of the SmPC. If appropriate, overdose should be included as a safety concern and appropriate risk minimisation proposed in the relevant part of the RMP.

<Potential for transmission of infectious agents>

This is only relevant for medicines for which the safety evaluation on Adventitious Agents has concluded on the possibility of a risk.

<Potential for misuse for illegal purposes>

The two most important areas are whether the drug is likely to be sold on the black market or used to enable assault.

Comment on the likelihood based on the substance and mechanism of action, and whether this translates to a safety concern that should be addressed in the RMP.

Potential for medication errors

Only summarise if the MAH’s view in relation to potential for medication errors are inadequate.

Consider the following points:

* Is the MAH’s analysis on medication errors which have occurred in the clinical trial population adequately reflected in the RMP?
* Availability of multiple strengths, posologies or concentrations, or where different products have different formulations, reconstitution differences etc, should be considered in the potential for medication errors.
* If a device is involved, has the MAH adequately analysed possible consequences of a device failure?

Assess if medication error constitutes a safety concern and whether there have been sufficient measures put in place to minimise the risk of medication errors. If appropriate, medication error should be included as a safety concern (important identified or potential risk).

Potential for off-label use

Only summarise if the MAH’s view in relation to potential for medication errors are inadequate.

Have situations where the product could intentionally be used outside the authorised indication (e.g. other disease area or target population) been adequately reflected in the RMP?

In cases where off-label use has the potential for harm beyond the safety profile of the product in the target population, this should be considered for inclusion as an important potential risk.

Specific paediatric issues

Issues identified in paediatric investigation plans.

Potential for paediatric off-label use – including non-authorised paediatric age groups; are there particular concerns for paediatric off-label use?

Comment here if any of the safety issues in paediatrics should be considered as a safety concern in the RMP.

*Identified and potential risks*

This module of the RMP should provide information on the important identified and important potential risks associated with use of the product. These include the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1 in GVP). The most clinically significant risks and/or those where further characterisation of the risk is required post-authorisation should be included as important identified or important potential risks. Often these are reflected in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC).

For RMPs covering multiple products where there are significant differences in the identified and potential risks for different products, it should be clear which risks relate to which product. Division of identified and potential risks using the headings below should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion. Headings which could be considered include:

<Risks related to a specific formulation, indication or route of administration>

Examples might include an RMP with two products with completely different indications: e.g. sildenafil with an indication in one product for erectile dysfunction and in a second product for pulmonary arterial hypertension.

<Risks relating to a specific target population>

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

The entire description of each safety concern from the RMP should not be copied in the assessment report. For each safety concern presented by the MAH, (), briefly comment on whether a proposed safety concern is appropriate (and therefore to be forwarded to the next section on Summary of Safety Concerns) or not. If yes, comment also briefly on the adequacy of the more detailed description of the safety concern.

*Identified and potential interactions*

This part includes Identified and potential pharmacokinetic and pharmacodynamic interactions in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. Important interactions with herbal medicines or with food should also be considered. A cross-reference to the Overview AR is normally appropriate.

If a specific comment beyond the discussion included in section 3.4.8 of the Overview AR is made here, comments in both sections should be made consistent. If warranted, specific interactions should be considered as a safety concern.

*Missing information*

This section should be built in relation to section “Populations not studied in clinical trials” and other data gaps e.g. long-term safety.

* 1. Summary of the safety concerns

**Table SVIII.1: Summary of the Safety Concerns**

|  |  |
| --- | --- |
| **Summary of safety concerns** |  |
| Important identified risks | <List here> |
| Important potential risks | <List here> |
| Missing information | <List here> |

Considering the data in the safety specification, the safety concerns listed above are appropriate.

or

<The following issues should be addressed :>

<X should also be <a> safety concern(s)>

<X should not be <a> safety concern(s)>

If the second option is chosen, the issues to be addressed must be included in the Request for supplementary information section.

* 1. Pharmacovigilance plan

Within this section, it should be assessed whether the MAH has discussed how the safety concerns from Module SVIII are proposed to be addressed within the pharmacovigilance plan and whether all areas requiring further investigation have been identified. See further details under Overall conclusions on the PhV Plan.

**Table Part III.3.1: On-going and planned additional pharmacovigilance activities**

| Activity/Study title (type of activity, study title [if known] category 1-3)\* | Objectives | Safety concerns addressed | Status  (planned, started) | Date for submission of interim or final reports (planned or actual) |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |

\*Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Comment briefly as to whether all studies are in the correct category.

* **Category 1 studies**, i.e. those that are considered key for the benefit–risk balance, should also be included as conditions of the MA (Annex II). These are studies where confirmation or identification of a safety concern could lead to major regulatory action including suspension or revocation of the MA.
* **Category 2 studies** are those imposed as specific obligations in the context of a conditional MA or MA under exceptional conditions(Annex II).
* **Category 3 studies**: These activities may include trials or studies which are already on-going (e.g. from clinical trials where the activity would be to provide a report) or be planned where the activity is to conduct the study. Category 3 studies/activities would include studies or activities requested by another Regulatory authority where the results are expected to provide information relevant to existing areas of uncertainty. Studies which have been specifically requested by the CHMP/PRAC (which are not conditions of the MA) or which may be suggested by the MAH to investigate a safety concern should also be included here. Studies to measure the effectiveness of risk minimisation measures would also normally fall into this category.

Comment on the usefulness of the study/activity to address the safety concern for category 1, 2 and 3 studies only.

The applicant should provide information on the study population, clear milestones and due dates, submission of interim results or other intermediate milestones, if requested.

If a study aims to evaluate the effectiveness of risk minimisation measures, this needs to be made explicit in the study summary of objectives.

Comment on the appropriateness of milestones and due dates for category 1, 2 and 3 studies only.

*Overall conclusions on the PhV Plan*

The PRAC rapporteur should consider the following points when writing the overall conclusions on the PhV plan:

* For all safety concerns identified in the safety specification, is routine PhV sufficient?
* Are additional PhV activities required for any safety concern? I If yes, are the additional PhV activities proposed by the MAH appropriate, clearly defined and described and suitable for further identifying or characterising risks or providing missing information? Are there additional activities proposed by the PRAC rapporteur?
* Do the objectives of the activities align with the identified / potential risks / missing information requiring confirmation or further investigation?

*Use this statement during the procedure only:*

There are still outstanding issues regarding the RMP but a preliminary view is that:

Use the following statements both during the procedure and at the time of Opinion:

When no additional PhV studies are proposed:

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

or

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

or

The proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and additional PhV studies/activities should be proposed as detailed in the Request for supplementary information.

Or if nothing has been proposed and a post-authorisation plan is considered necessary:

A post-authorisation pharmacovigilance development plan is required.

Finally add the statement about the need for studies to measure effectiveness. Choose one of the following:

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

or

The study(ies) in the post-authorisation development plan <is><are> sufficient to monitor the effectiveness of the risk minimisation measures.

or

There is a need for a study to monitor the effectiveness of <> state which additional risk minimisation measures should be studied(please refer to the section on Request for supplementary information).

*<Plans for post-authorisation efficacy studies >*

**Table Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study  (type and study number) | Objectives | Efficacy concerns addressed | Status  (Planned, started, completed, results submitted) | Date for submission of interim or final reports (planned or actual) |
|  |  |  |  |  |
|  |  |  |  |  |

Comment if needed. The need of PAES will be raised by the CHMP. No in-depth assessment is expected from the PRAC Rapporteur.

Please consider that text from the table below will be included verbatim in the RMP public summary.

* 1. Risk minimisation measures

*Routine risk minimisation measures*

Table Part V.1: Description of routine risk minimisation measures by safety concern

|  |  |
| --- | --- |
| Safety concern | Routine risk minimisation activities  Please provide the following information, as applicable: |
| <Safety concern 1> | <Routine risk communication:>  Provide only reference to SmPC/PL section(s) (do not copy the complete SmPC/PL wording):  e.g. <SmPC section 4.8.>  e.g. <PL section 4>  <Routine risk minimisation activities recommending specific clinical measures to address the risk:>  Include the specific clinical measures/monitoring information for healthcare professionals in SmPC or patients in PL:  e.g. <recommendation for liver function monitoring are included in SmPC sections 4.4>  e.g. <how to detect early signs and symptoms of serious infections in PL sections 2 and 3>  <Other routine risk minimisation measures beyond the Product Information:>  <Pack size:>  e.g. when the amount of medicine in a pack helps ensuring that the medicinal product is used correctly.  <Legal status:>  e.g. restricted medical prescription, special medical prescription, categorisation at member states level etc. |

Please make sure all safety concerns from Part II: Module SVIII are listed above.

Comment if needed

*<**Additional risk minimisation measures>*

State which additional risk minimisation measures are proposed by the MAH, whether they are needed and which safety concerns they address. Are there additional activities proposed by the PRAC rapporteur? Additional risk minimisation measures should only be included in the RMP if the proposed measures are necessary for the safe and effective use of the product. Request the MAH to remove any items which do not meet this criterion.

*Overall conclusions on risk minimisation measures*

Use this statement during the procedure only:

There are still outstanding issues regarding the RMP but a preliminary view is that:

Use the following statements both during the procedure and at the time of Opinion:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

or

The proposed risk minimisation measures are not sufficient to minimise the risks of the product and supplementary risk minimisation measures are required relating to:

List safety concerns and reflect any questions in the Request for supplementary information section.

or (when the risks cannot be brought to a satisfactory level)

The proposed risk minimisation measures are not sufficient to minimise the risks of the product in the proposed indication(s).

* 1. Elements for a public summary of the RMP

Refer to the elements for a public RMP summary in section VI of the RMP which includes key elements of the RMP in lay language and consider whether there are any updates to the RMP which need to be reflected in this section.

Consider whether:

* any updates to the following sections are balanced and suitable for publication:

- VI.2.1 Overview of disease epidemiology

- VI.2.2 Summary of treatment benefits

- VI.2.3 Unknowns relating to treatment benefit

* tables in Part VI have been updated appropriately
* the summary of updates to the RMP over time is accurate and has been updated appropriately ( including whether this current update qualifies for inclusion in the table).

The elements for a public summary of the RMP <require><do not require> revision following the conclusion of the procedure:

* 1. Annexes

Check to see whether annexes have been updated accordingly and comment on this.

The annexes have <not> been updated appropriately <and the following further changes are recommended: