EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation

Guidance on the format of the risk management plan (RMP) in the EU – in integrated format

General consideration and guidance

This guidance should be read in conjunction with GVP module V.

According to GVP module V, the aim of a risk management plan (RMP) is to document the risk management system considered necessary to identify, characterise and minimise the important risks of a medicinal product. To this end, the RMP contains:

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

Throughout this document, please be as concise as possible and ensure the content is scientifically based and that it does not include any element of a promotional nature. Consider which information will add value to the readers' understanding of the safety profile of the medicinal product and how best to interpret and manage the important identified and potential risks as well as the uncertainties surrounding the information available. Please focus the document accordingly. Tabulation of any data is encouraged if it aids the presentation.

The applicant/marketing authorisation holder should include links or references to the relevant part of the eCTD dossier of the supporting documents or PSURs, when applicable. Throughout the RMP template, eCTD data/submissions should be read as eCTD or CTD data/submission, corresponding to the type of submission to the competent authority. Specific requirements for different types of initial marketing authorisation applications are described within each section of the template.

The examples provided in each Module/Section represent only guidance for writing the RMP and should not be regarded as directions in a defined scenario. Each RMP should be based on the safety data of the medicinal product.

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Checklist for writing or assessing an RMP

The following general points need to be considered when writing or reviewing an RMP for a medicinal product. The checklist is meant to provide further guidance and is not part of the RMP; therefore, it should not be included in the documents submitted for assessment:

Part II: Safety specification

- ✓ *Have all appropriate parts of the safety specification been included?*
- ✓ *Have all appropriate data been reviewed when compiling the safety specification, e.g. are there important (outstanding) issues which have not been discussed in the safety specification?*
- ✓ *If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?*
- ✓ *Have limitations in the safety database (e.g. related to the size of the study population, study inclusion and exclusion criteria) been considered and what are the implications of such limitations on the safety profile of the medicinal product? Has reference been made to populations likely to be exposed during the intended or expected use of the medicinal product in the medical practice? Does the safety specification provide a true reflection of the safety concerns (e.g. important identified risks, important potential risks and/or missing information) with the medicinal product?*
- ✓ *For generic or hybrid applications, have all safety concerns from the latest version of the RMP for the reference medicinal product or from a list of safety concerns published on the CMDh website been included in the safety specification? If not, has appropriate justification been provided and has the applicant proposed a list of safety concerns? If no information on the safety profile of the reference medicinal product is available (no RMP or no CMDh list for the substance), has the safety profile been drafted considering all available relevant information (e.g. public assessment documents for the reference medicinal product, literature, applicant's own trial data)?*

Part III: Pharmacovigilance plan

- ✓ *Are all safety concerns from the safety specification covered in the pharmacovigilance plan?*
- ✓ *Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?*
- ✓ *Are the activities in the pharmacovigilance plan clearly defined, described and suitable for identifying or characterising risks or providing missing information?*
- ✓ *Are the safety studies that have been imposed by a competent authority as conditions clearly identified?*
- ✓ *If there are safety concerns derived from medication errors, does the RMP include appropriate proposals to monitor the correct use of the product?*
- ✓ *Are the proposed additional studies necessary, feasible, non-promotional and able to provide the required further characterisation of the risk(s) and address the scientific questions?*
- ✓ *Are timelines and milestones appropriate and feasible for the proposed actions, including those for the submission of results?*

Part IV: Plans for post-authorisation efficacy studies

- ✓ *Have all post-authorisation safety studies (PAES), either as conditions of the marketing authorisation or as specific obligations, been included?*

Part V: Risk minimisation measures

- ✓ *Are routine risk minimisation measures sufficient or is there a need identified for additional risk minimisation activities?*
- ✓ *Have additional risk minimisation activities been suggested and, if so, are these sufficiently justified and risk-proportionate? Is implementation feasible in all Member States?*
- ✓ *Have criteria for effectiveness of additional risk minimisation activities been defined a priori?*
- ✓ *Are the methods for evaluating the effectiveness of risk minimisation activities well described and appropriate?*

Part VI: Summary of the risk management plan

- ✓ *Is it a true representation of the RMP?*
- ✓ *Have the facts been presented appropriately without any elements of promotional nature?*

EU Risk Management Plan for <Invented name> (INN or common name)

RMP version to be assessed as part of this application:

RMP Version number: <Insert number>

An RMP should be assigned a new RMP version number and a date each time the RMP is updated and submitted for assessment (e.g. versions 0.1, 0.2, 0.3 etc. for an initial submission of an RMP; versions 1.1, 1.2, etc. and 2.1, 2.2 etc. for RMP updates post-authorisation).

The version number of the RMP version agreed at the time of the competent authority opinion should be the same as the one provided with the last eCTD submission in the procedure (most often with the closing sequence). It is advisable to use major version numbers for final approved RMP versions (e.g. version 1.0 at the end of the initial marketing authorisation application; 2.0, 3.0, etc. for post-authorisation updates).

Data lock point for this RMP: <Enter a date>

It is recommended that the Data Lock Point (DLP) should not be more than 6 months before the RMP sign-off date.

For initial marketing authorisation applications it usually reflects the DLP of the Clinical Safety Summary.

Date of final sign off: <Enter a date>

Rationale for submitting an updated RMP: <Not applicable for initial marketing authorisation application submission>

Summary of significant changes in this RMP: <Add high level description of major changes to each module>

<Other RMP versions under evaluation:>

This section is applicable for post-authorisation RMP updates when a different RMP version is still under assessment with another procedure.

If two or more parallel procedures contain RMP submissions, to facilitate assessment, it is usually advised to submit a common consolidated version of the RMP; the supporting Word version of the RMP included with the submission should include track changes (colour coded for each procedure), so that changes related to each procedure can be easily identified. This will also facilitate the finalisation of the RMP for each procedure.

Where the submission of a common, consolidated RMP version is not practical, distinct RMP documents may be submitted with each procedure (Word versions should also include tracked changes, per procedure). For further guidance please refer to European Medicines Agency post-authorisation procedural advice for users of the centralised procedure[1]. The best regulatory path for the RMP update in case of multiple procedures potentially impacting on the RMP content should be discussed with the competent authority before submissions.

RMP Version number: <Insert number>

[1] available on EMA website http://www.ema.europa.eu

Submitted on: <Enter a date>

Procedure number: <indicate procedure number>*, if already assigned.*

<Details of the currently approved RMP:> *This section is not required for initial marketing authorisation applications.*

There can only be ONE currently approved RMP for a product(s).

If several updates to the RMP are submitted during the course of a procedure, the version considered as the "current" approved RMP for future updates and track-changes purposes shall be the one mentioned in the Opinion documents (most often same version is submitted with the closing sequence of the procedure).

Version number: <enter a version number>

Approved with procedure: <enter a procedure number>

Date of approval (opinion date): <dd/mm/yyyy>

QPPV name[2]:

The QPPV´s actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalised approved version of RMP; for eCTD submission, this would be the RMP with the last eCTD sequence of the procedure (usually the closing sequence).

Select one of the options:

QPPV signature:

Or

QPPV oversight declaration: <The content of this RMP has been reviewed and approved by the marketing authorisation <holder´s> <applicant´s> QPPV. The electronic signature is available on file.>

[2] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	
Pharmacotherapeutic group(s) (ATC Code)	
Marketing Authorisation <Holder> <Applicant>	*Name of the marketing authorisation applicant for initial marketing authorisation applications.* *For mutual recognition/ decentralised procedures applications include also information on expected future marketing authorisation holders in the reference member state, if this information is known at the time of the application.*
Medicinal products to which this RMP refers	
Invented name(s) in the European Economic Area (EEA)	*For decentralised/mutual recognition products include only the invented name(s) in the reference member state.*
Marketing authorisation procedure	<centralised> <mutual recognition> <decentralised> <national>
Brief description of the product	Chemical class
	Summary of mode of action
	Important information about its composition *(e.g. origin of active substance for biologicals, relevant adjuvants or residues for vaccines)*
Hyperlink to the Product Information	*Include a link or reference to the proposed PI in the eCTD sequence.* *If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s) in the EEA	Current (if applicable):
	Proposed (if applicable): *e.g. if the RMP is submitted with an extension/restriction of indication*
Dosage in the EEA	Current (if applicable): *Summarise information only related to the main population; not a duplication of all dosages/dosage adjustments for the sub-populations listed in SmPC section 4.2.*

	Proposed (if applicable): *Summarise information only related to the main population; not a duplication of all dosages/dosage adjustments for the sub-populations listed in SmPC section 4.2.*
Pharmaceutical form(s) and strengths	Current (if applicable):
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	Yes/No *At initial marketing authorisation application conclusion or with RMP updates*

Part II: Safety specification

For full initial marketing authorisation applications, all modules in Part II should be submitted. The requirements for other types of initial marketing authorisation applications are provided in section V.C.1.1 of the GVP – Module V.

If a reference medicinal product is authorised, please check if it has an RMP/summary for the RMP published on the EMA[3] and/or national competent authorities' website or whether the safety concerns for a substance/reference product are published on the CMDh[4] website. If the Applicant considers that the available evidence justifies the reclassification or removal of a safety concern, this should be discussed. Similarly, if the Applicant has identified a new safety concern specific to the product (e.g. risks associated with a new formulation, route of administration or new excipient; or a new safety concern raised from any clinical data generated), this should be also discussed and the new safety concern detailed in Module SVII.

Article 14(2) of Regulation (EC) No 1394/2007 provides for a specific framework for RMP for advanced therapy medicinal products (ATMP). The marketing authorisation applicants/holders should adapt the risk management plans of ATMP, considering and discussing the anticipated post-authorisation follow-up needs, focusing on particularities of these medicinal products. The specific RMP content requirements for ATMP should be discussed with the competent authority before the submission.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

This section should only contain data relevant for the identification of the safety concerns (see module SVII).

Information on inter-regional (e.g. EU, US, Asia, Africa etc.) variations may be provided when relevant, but the focus should be on the European population. A brief summary of epidemiology is expected to be provided. This summary should provide an interpretive, high level overview of the information avoiding detailed discussion on specific epidemiology studies or published articles.

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
[4] http://www.hma.eu/464.html

When the medicinal product has/is expected to have several authorised indications, the data for the different indications should be integrated where this is sensible from a clinical perspective. When there are clinically relevant differences in user characteristics between the authorised indications, separate sections are, however, expected for each authorised indication (e.g. Crohn's disease and rheumatoid arthritis; multiple sclerosis and hairy cell leukaemia).

This module may not be applicable or have a reduced content for RMPs submitted with initial marketing authorisation applications involving:

- *Generic medicinal products;*
- *Fixed combination medicinal products which do not contain a new active substance;*
- *"Well established medicinal use" medicinal products;*
- *Biosimilar medicinal products.*

For hybrid medicinal products, the requirements are based on risk proportionality principle, addressing the differences with the "originator" product.

<Indication>

Incidence:

Prevalence:

Demographics of the population in the <authorised> <proposed> indication – <age, gender, racial and/or ethnic origin> *(when relevant for assessment of safety and risk management)* and risk factors for the disease:

The main existing treatment options: *summarise the standard of care, with the view of the expected safety profile and outcome in the absence of treatment with the medicinal product*

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

Discuss the possible stages of disease progression to be treated and applied to the natural history of the indication in the (untreated) population. This section should also describe concisely the relevant adverse events to be anticipated in the (untreated) targeted population in EU, their frequency and their characteristics.

Important co-morbidities:

The risks of the medicinal product are evaluated based on the characteristics of the medicinal product (e.g. documented in clinical trials) and the context of use: expected co-morbidities and co-medications in the target population.

This section should include, where clinically relevant, diseases distinct from the indication that occur frequently in patients with the indicated condition (e.g. hypertension is a co-morbidity for hyperlipidaemia); a simple list is sufficient.

For guidance on when information should be provided on co-morbidities in the target population, please consider the following examples:

- *If the target population for a medicinal product is men with prostate cancer, the target population is likely to be men over the age of 50 years, and they have an increased risk for myocardial infarction.*

- *Patients with psoriasis are at an increased risk of depression and suicidal ideation and behaviour.*

Part II: Module SII - Non-clinical part of the safety specification

This module should present a high-level summary of the significant non-clinical safety findings. The topics should normally include, but do not need to be limited to:

Key safety findings from non-clinical studies and relevance to human usage: *(for each safety finding)*

Toxicity

- key issues identified from acute or repeat-dose toxicity studies
- reproductive/developmental toxicity
- genotoxicity
- carcinogenicity

Safety pharmacology *as applicable*

- cardiovascular system, including potential effect on the QT interval
- nervous system
- etc.

Other toxicity-related information or data *as applicable*

What constitutes an important non-clinical safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Normally, significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans should be discussed. Also, quality aspects, if relevant to safety (e.g. genotoxic impurities), should be discussed. If a medicinal product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population should be discussed. Based on these discussions, the applicant should comment if there are any findings in the non-clinical testing warrant inclusion among the summary of safety concerns; i.e. being an important identified risk, important potential risk, or if a non-clinical study is missing information.

Where studies do not raise concerns in relation to human safety, these should be mentioned, if relevant, to the target population (e.g. no signs of reproductive or developmental toxicity if the medicinal product is intended for use in women of childbearing age).

For full initial marketing authorisation applications where the Applicant generated no non-clinical data, relevant data available from bibliographical sources should be presented.

Where the non-clinical safety finding is not considered relevant for human beings, the provision of a brief explanation is required, and the safety finding is not expected to be carried forward to SVII and SVIII as a risk.

If, based on the assessment of the non-clinical or clinical data, additional non-clinical studies are considered warranted, this should be briefly discussed here.

In the Post-authorisation phase, this section would only be expected to be updated when new non-clinical data impact the list of safety concerns. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed when sufficient relevant post-marketing experience and evidence are gathered can be removed from the list of safety concerns.

This module may not be applicable or have a reduced content for RMPs submitted with initial marketing authorisation applications involving:

- *Generic medicinal products;*

- *Hybrid medicinal products;*
- *"Well established medicinal use" medicinal products.*

For fixed combination medicinal products with a new active substance, the focus of this module should be on the data generated for the new active substance. For fixed combination medicinal products with no new active substance, the module should contain information on the new non-clinical data generated, if any.

Part II: Module SIII - Clinical trial exposure

In this module, in order to assess the limitations of the human safety database, summary information on the clinical trial exposure should be provided in an appropriate format (e.g. tables/graphs) at time of submission of the initial RMP or when there is a major update due to new exposure data from clinical studies (e.g. in a new indication). The content of this section should be assessed for relevance over time and, in the absence of new significant clinical trial exposure data, this section does not need to be updated.

Data should be pooled and not shown per individual trial unless there are clearly relevant and duly justified reasons why some data cannot be pooled or combined.

If the RMP includes more than one medicinal product, the total population table should be provided for each medicinal product as well as a table that combines the information on total patients exposed for all medicinal products, as appropriate.

The cumulative exposure data in this module (including cumulative data per indication, treatment duration, patient population, formulation), when presented in an aggregated form, would not be deemed to be commercially confidential and thus would not be redacted in case of an access to document request (unless a detailed justification is provided which demonstrate how the release of the data would undermine the commercial interests or competitive position of the company)[5].

The categories below are suggestions; tables/graphs should be tailored to the product according to the availability of data:

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time
e.g. <1 m		
1 to <3 m		
3 to <6 m		
≥6 m etc.		
Total person time		
<Indication>		
Duration of exposure	Patients	Person time
e.g. <1 m		
1 to <3 m		

[5] Same principle applied as in EMEA/743133/2009: HMA/EMA Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs); available on EMA website http://www.ema.europa.eu

3 to <6 m		
≥6 m etc.		
Total person time for indication		

Table SIII.2: Age group and gender

When providing data by age group, the age group should be relevant to the target population; this should be reflected in the choice of age categories for this table. Paediatric data should be divided by age categories (e.g. ICH-E11[6]); similarly, the data on older people should be stratified into age categories reflecting the target population (e.g. 65-74, 75-84 and 85 years and above).

Age group	Patients		Person time	
	M	F	M	F
e.g. Preterm newborn infants				
Term newborn infants (0 to 27 days)				
Infants and toddlers (28 days to 23 months)				
Children (2 to e.g. 11 years)				
Adolescents (e.g. 12 to 17 years)				
Adults (e.g. 18 to 64 years)				
Elderly people				
65-74 years				
75-84 years				
85 + years				
Total				
<Indication 1>				
Age group	Patients		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table SIII.3: Dose

Dose of exposure	Patients	Person time
Dose level 1		
Dose level 2 etc.		
Total		
<Indication 1>		
Dose of exposure		
Dose level 1		
Dose level 2 etc.		
Total		

[6] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590

Other stratifications should be provided where this adds meaningful information for risk management planning purposes (e.g. ethnic origin).

Table SIII.4: Ethnic origin

Ethnic origin	Patients	Person time
<Indication 1>		
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

This module may not be applicable or have a reduced content for RMPs submitted with initial marketing authorisation applications involving:

- *Generic medicinal products;*
- *"Well established medicinal use" medicinal products.*

For fixed combination medicinal products with a new active substance, the focus of this module should be on the data generated for the new active substance. For fixed combination medicinal products with no new active substance, the module should contain information on the new non-clinical data generated, if any.

For hybrid medicinal products, the requirements are based on risk proportionality principle, addressing new data generated and the differences with the "originator" product.

Part II: Module SIV - Populations not studied in clinical trials

This module should discuss the populations which have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the medicinal product in the marketplace should be explicitly discussed.

Exclusion criteria from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indication (e.g. "on-label"). When such populations are proposed as missing information, RMP module SIV should then also include a discussion on the relevant subpopulations, including whether or not any use in populations excluded from the clinical trials (e.g. women of childbearing potential, older people) might be associated with additional risks of clinical significance in case the product is used in these populations.

This module should discuss the limitations of the clinical trial population in relation to predicting the safety of the medicinal product(s) in real life use. If difficult to populate for e.g. for bibliographic applications or where the applicant does not have access to original trial data, the Applicant is encouraged to include any relevant data that the Applicant has access to, even if these are limited to the inclusion/exclusion criteria listed in published studies which are publicly available.

This module may not be applicable or have a reduced content for RMPs submitted with initial marketing authorisation applications involving:

- *Generic medicinal products;*
- *Hybrid medicinal products;*
- *Fixed combination medicinal products with no new active substance;*
- *"Well established medicinal use" medicinal products.*

For fixed combination medicinal products with a new active substance, the focus of this module should be on the data generated for the new active substance.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Discuss the important exclusion criteria in the pivotal clinical studies across the development programme.

<Criterion>

Reason for exclusion:

Is it considered to be included as missing information?: <Yes>/<No>

Rationale: *(if not included as missing information)*

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

It is assumed that the clinical trial development programme is unable to detect certain kinds of adverse reactions. In these circumstances, please add a simple statement indicating the particular limitations of the programme (choose options that apply):

<The clinical development programme is unlikely to detect certain types of adverse reactions such as <rare adverse reactions>, < adverse reactions with a long latency>, or those caused by <prolonged> or <cumulative exposure>.

Or, if this assumption is not correct, briefly discuss the level of detection for the clinical trial programme conducted.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Some populations are often excluded or under-represented in clinical trials. For each of the line in the table below, indicate the information on the low exposure of or the lack thereof (e.g. the number of subjects included and total person years of follow-up in the clinical development programme) for the medicinal product(s) covered in this RMP, if available and as appropriate.

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population *Please indicate if included in pre-authorisation clinical development program:*	**Exposure** *Total number of subjects and person time*
Pregnant women	<not included in the clinical development program> *In most cases, person time exposure data can be omitted for this population*
Breastfeeding women	

Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	<not included in the clinical development program> *The degree of impairment should be specified, if available*
Population with relevant different ethnic origin	<not included in the clinical development program>
Subpopulations carrying relevant genetic polymorphisms	<not included in the clinical development program> *Type of genetic polymorphism should be specified, if available*
Other *If applicable, other special population under-represented in clinical trials which are relevant for the targeted indication if the safety profile is expected to be different to the general population.*	<not included in the clinical development program>

Part II: Module SV - Post-authorisation experience

This module is normally empty before the granting of the Marketing Authorisation unless post-marketing data are available from post-authorisation experience in other regions outside EU where the product is already authorised or from other authorised medicinal products containing the same active substance from the same marketing authorisation holder.

This section should only provide an overview of exposure in the post-authorisation phase for risk management planning purposes. It is not the intention to duplicate post authorisation experience information from PSURs but to provide high-level information on the number of patients exposed post authorisation.

A discussion on how the medicinal product is being used in practice and on-label and off-label use, including use in the special populations mentioned in RMP module SIV, can also be included when relevant for the risk identification discussion in module SVII.

Where appropriate and relevant for the discussion in SVII, data on use in markets outside the EU from indications not authorised in EU should also be summarised, and the implications for the authorisation in the EU should be discussed.

This module may not be applicable or have a reduced content in the same situations as Module SIV, described above.

SV.1 Post-authorisation exposure

When available, worldwide data on patients exposed post marketing should be provided. For post-marketing RMP updates, this section should be updated only when the cumulative post-marketing

exposure changes to a degree where the considerations on the risk evaluation need also to be updated (e.g. population exposed in a new indication). Details and methods used to calculate person- and person-time exposure should be briefly presented; however, this section is not intended to duplicate the information already available in the PSUR and should only be presented as an overview.

The standard method to calculate exposure based on the posology of the product and/or treatment cycles and sales and global exposure data presented in an aggregated form would not be deemed to be commercially confidential and thus would not be redacted in case of a access to document request (unless a detailed justification is provided which demonstrate how the release of the data would undermine the commercial interests or competitive position of the company)[7]. The redaction would be accepted for data pertaining to national exposure data, if proposed.

SV.1.1 Method used to calculate exposure

If different methods have been used to calculate exposure for some tables, this section should be repeated before each of the relevant table(s).

SV.1.2 Exposure

It is acknowledged that post-marketing data will most likely not be available by age group or by gender but, when available, this should be provided. Total exposure and exposure by indication should always be presented.

Table SV.1: Exposure table by indication, <gender>, <age group>, <region>

The categories provided may follow template from GVP Module VII – Periodic safety update report[8], and the PSUR table(s) can be reused in this RMP module. Other relevant variables should be used if relevant for the risk identification discussion, e.g. duration of treatment.

If possible, use in the EU should be broken down by country or sales area. Exposure from areas outside of the EU for indications different than those approved or proposed in the EU should be presented as a separate section in the table, if exposure in such patients is relevant for the safety discussion for the EU indication.

Indication	Sex		Age (years)				Dose		Formulation		Region		
	Male	*Female*	*e.g. ≥2 to ≤16*	*e.g. >16 to 65*	*e.g. >65*	*e.g. unknown*	*e.g. <40*	*e.g. Unknown*	*e.g. Intravenous*	*e.g. Oral*	*e.g. EU country*	*e.g. Non EU country*	*e.g. Other*
Overall													
<Indication1>													
<Indication2>													

[7] EMEA/743133/2009: HMA/EMA Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs); available on EMA website http://www.ema.europa.eu

[8] available on EMA website http://www.ema.europa.eu

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Discuss the potential for misuse for illegal purposes, e.g. as a recreational drug or to facilitate assault. Discuss the means of limiting this in the risk minimisation plan where appropriate, e.g. limited pack size, controlled access programme, special medical prescription etc.

This module may not be applicable or have a reduced content in the same situations as Modules SIV-SV, described above.

Part II: Module SVII - Identified and potential risks

The safety profile of the product should be concisely presented, as it is known at the time of the RMP data lock point. Relevant information for the identification of important identified and important potential risks and any relevant updates on missing information should be discussed (see GVP Module V section V.A.1). If they have not already been provided in the previous sections, provide appropriate eCTD links or references to the primary data informing the discussion here.

The identification of the important identified and important potential risks in this section to be addressed in the RMP should not be a copy paste of tables or lists of adverse reactions from clinical trials or of sections 4.4 and 4.8 of the SmPC, as the safety concerns to be included in this section of the RMP should be considered important (see GVP Module V section V.A.1).

For RMPs including multiple substances and/or medicinal products and where there may be significant differences in the important identified and important potential risks or missing information for different substances/ medicinal products, it is appropriate to make it clear which safety concerns relate to which substance/ medicinal product. Categories to be considered include safety concerns relating to the active substance, safety concerns related to a specific formulation or route of administration and safety concerns associated with a switch to non-prescription status.

Exceptionally, if agreed with the competent authority and where needed for risk management planning purposes, the safety specification may include additional elements if they are resulting in important identified risk, important potential risk or missing information such as:

- *The disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches);*
- *Innovative pharmaceutical forms (e.g. to contain a higher percentage of active substance which reduces the dose burden for patient and related side effects; long-term delivery gastric-resident dosage forms for ultra-long-acting drug delivery may improve patients adherence to treatment and to reduce the gastro-intestinal side effect);*
- *Use with a medical device and risks associated with the medical device;*
- *Quality aspects relevant in relation to the safety of the product and not adequately addressed at time of marketing authorisation (e.g. investigation of other methods to improve the quality/composition of the product to address adverse events related to it).*

See GVP Module V section V.B.5.8. for the safety topics derived from specific situations/data sources which are thought to be of particular interest to be discussed in module SVII when they lead to risks of the medicinal product, as appropriate.

Advanced therapy medicinal products (ATMP): Article 14(2) of Regulation (EC) No 1394/2007 provides for a specific framework for RMP for advanced therapy medicinal products (ATMP). The marketing authorisation applicants/holders should adapt the risk management plans of ATMP, considering and discussing the anticipated post-authorisation follow-up needs, focusing on particularities of these medicinal products. The specific RMP content requirements for ATMP should be discussed with the competent authority before the submission. Further guidance on the safety and efficacy follow-up and risk management requirements for ATMP is provided on the Agency website[9]. See the Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products[10] for risks to be considered in drafting the safety specification.

For hybrid medicinal products, the requirements are based on risk proportionality principle, addressing the differences with the "originator" product.

Generic medicinal products and fixed combination medicinal products with no new active substance

This module is applicable for all initial marketing authorisation applications except for applications for generic medicinal products and fixed combination medicinal products with no new active substance, if there is a RMP available for the reference medicinal product or when the reference medicinal product does not have an RMP but the safety concerns of the substance are published on the CMDh website[11].

In case a reference medicinal product has published RMP/summary of the RMP on the EMA[12] and/or national competent authorities' website or the safety concerns for a substance/reference product are published on the CMDh[13] website, than the safety concerns should be based on it. If discrepancies exist between approved RMPs and/or lists of safety concerns for the same active substance, then the applicant is expected to propose and justify the most appropriate safety specification for their medicinal product. Exceptionally, the applicant for a new generic medicinal product may add, reclassify or remove safety concerns compared with the safety profile of the reference product if this is appropriately justified.

In case of any changes to the already included information in the published CMDh list, the marketing authorisation holder should provide the information to CMDh using the instructions on their website[14] once the RMP is approved.

In very exceptional circumstances, if Module SVII is not applicable and a change in the safety specification is proposed, include the following:

<Justification of <new safety concerns> <and/or reclassification> with a submission of this RMP in comparison with the reference medicinal product published on <EMA/national competent authority/CMDh> website>:

Please consider that the text in this section will be included verbatim in the RMP public summary.

<<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>>

[9] See www.ema.europa.eu; further ATMP-specific guidance is being developed
[10] EMEA/149995/2008; available on EMA website http://www.ema.europa.eu
[11] http://www.hma.eu/464.html
[12] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
[13] http://www.hma.eu/464.html
[14] http://www.hma.eu/464.html

<Changes in the level of scientific evidence for the causal association or risk-benefit impact including risk factors and risk groups – *use text from SmPC and discuss briefly*>

SVII.1 Identification of safety concerns in the initial RMP submission

This section is expected to be "locked" and not change after the approval of the initial RMP.

Whether a risk is considered identified risk or potential risk would depend on the strength of evidence supporting the causal association with the medicinal product.

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

Risks for adverse reactions may be identified from multiple sources such as non-clinical findings confirmed by clinical data; clinical trials, epidemiological studies, spontaneously reported data and published literature, for example:

- *An adverse reaction recorded in a well-designed randomised clinical trial in excess of the placebo comparator would generally be considered as an identified risk if the criterion on clinical outcome is also fulfilled;*
- *For some adverse reactions (e.g. laboratory abnormalities), the identified risk may be the clinical outcome of the adverse reaction, if these have been observed (e.g. associated with such laboratory abnormality). For example: the identified risk of bleeding due to abnormal INR range/thrombocytopenia, the identified risk of infection due to neutropenia, the identified risk of hypotension/ lipothymia/ renal failure due to adverse reactions such as dehydration as a consequence of vomiting and/or diarrhoea, the identified risk of cardiac arrhythmia due to coronary vasospasm or Torsade de Pointes due to QTc prolongation.*

From the potential risks of the medicinal product, the RMP should address only the risks with 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. For example:

- *Where the supposition is based on more than theoretical considerations, may include signals that have been evaluated with an indeterminate outcome (i.e. which can be neither refuted nor confirmed), a class effect plausible also for a new medicinal product, findings from non-clinical studies which have not been observed in clinical studies, or undesirable clinical outcomes observed in clinical trials or epidemiological studies for which there is not yet enough evidence to support a causal relation (e.g. due to low number of events or unexpected incidence rates in comparator groups).*

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns for the purpose of risk management planning (see GVP Module V section V.A.1). For example:

- *"Transient low-grade headache" is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk.*
- *"Reversible alopecia", "itchy rash" or "transient reduced fertility" of a medicinal product indicated for the treatment of life-threating oncologic diseases are risks that could have an impact on the quality of life. However, the clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated and these risks should therefore not be classified as important.*
- *The risk of "irreversible reduction of fertility" is not considered important for a medicinal product almost exclusively used in a patient population aged > 60 years given the therapeutic context.*
- *Some risks are already well-known to health professionals and do not require additional pharmacovigilance activities or additional risk minimisation measures. For example, in cases where health professionals are already aware of the risk of anaphylactic reactions and have the appropriate measures in place as part of clinical practice, anaphylactic reactions may not need to be included as an important risk.*

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The justification for non-inclusion should be provided. The reasons can be grouped as described in examples below. Information on seriousness, frequency, or adherence to standard clinical practice (in each EU Member state where the product is authorised) should be provided to support the proposed classification, as appropriate:

<Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):>

<List of risks>

<Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:>

<List of risks>

<Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):>

<List of risks>

<Known risks that do not impact the risk-benefit profile>

<List of risks>

<Other reasons for considering the risks not important:>

<List of risks>

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

For risks included in the list of safety concerns of the medicinal product(s) for the purpose of risk management planning, the scientific evidence that has led to the inclusion should be briefly discussed. Further details on the safety concerns should be provided in section SVII.3.

Important risks to be included in the RMP are those risks which are already characterised and confirmed to have an impact on the risk-benefit balance of the medicinal product or those that, when further characterised and if confirmed to be associated with the medicinal product, would have an impact on the risk-benefit balance. These risks would usually warrant further evaluation as part of the pharmacovigilance plan or risk minimisation activities.

<Important Identified Risk 1>:

Examples of important identified risks are:

- *If an adverse reaction which is an important identified risk for an active comparator occurs at a similar or higher frequency with the new medicinal product in a clinical trial, this suggests that the adverse reaction may also be an important identified risk for the new medicinal product.*
- *For a medicinal product on the market for years, drug-induced liver injury was identified as a new adverse reaction after a referral procedure and considered to have a major impact on the benefit risk. Warnings in section 4.4. of the SmPC have been implemented and the recommendation to perform regular liver function tests have been added to the SmPC as a precautionary measure in the post-marketing period. "Hepatotoxicity" or a similar term should be classified as an important identified risk.*
- *Neutropenia of ≥ grade 3 and serious infections with fatal outcome were observed in clinical trials prior marketing authorisation of an oral "first-in-class" medication. Regular blood counts are recommended, according to the SmPC, to minimise the risk of serious infections. As oral medications are very likely to be used in an out-of-hospital setting and it is unclear whether this risk minimisation will be effective, "serious infections" should be included as an important identified risk.*
- *Cardiac disorders with life-threating outcome were identified as being causally related to a medicinal product in clinical trials prior marketing authorisation. However, an accurate estimation of frequency was not possible from clinical trial data as the clinical trial population was too small and, therefore, a PASS investigating frequency of the risk was imposed. Cardiac disorders should be classified as an important identified risk.*
- *If a serious adverse reaction was identified in clinical trials (e.g. Stevens Johnson Syndrome) and, at the time of the initial marketing authorisation application, the incidence is considered acceptable for a positive risk-benefit balance, routine pharmacovigilance activities could be considered sufficient to monitor this risk assuming that the event is appropriately managed by health professionals in clinical practice. The periodic risk-benefit evaluation (e.g. PSUR) will therefore discuss the findings from spontaneous reporting and provide an evaluation on whether the frequency of the event is higher than expected. However, if a signal is raised following the use in clinical practice, the identified risk would be considered as an important identified risk and additional pharmacovigilance activities should be considered to provide an accurate estimate of the frequency and inform the risk-benefit evaluation.*

Risk-benefit impact: *present the reasons for this classification, consider seriousness, frequency and severity as determinants, e.g.:*

- *Serious adverse reactions (as described in GVP Annex I – Definitions) that result in death, are life-threatening, result in persistent or significant disability or incapacity, or are a congenital anomaly/birth defect, if not prevented or managed appropriately;*
- *Common adverse reactions that are so severe (Grade 3-4) that it may lead to a serious outcome, discontinuing the treatment and/or reducing the efficacy of the medicinal product, if not managed appropriately, even if the adverse reaction is not serious;*
- *Severe adverse reactions occurring with high frequency in the targeted population that could have a severe impact on the patient (e.g. depression could significantly impact the quality of life and it could also lead to the potential risk of suicide, therefore, it could be classified as in important identified risk).*

<Important Potential Risk 1>:

Examples of important potential risks are:

- *QTc prolongation is a known adverse reaction of another medicinal product of the same class, observed in clinical trials and included in section 4.8 of the SmPC; however, no events of Torsade de Pointes have been observed in the clinical development programme or the magnitude of QTc prolongation is lower than normally associated with Torsade de pointes. Consequently, "Torsade de pointes" would be an important potential risk;*
- *When neutropenia is a listed adverse reaction, "serious infections" can still be classified as an important potential risk even if there is not yet enough clinical evidence of serious infections associated with neutropenia.*
- *When there is a high likelihood of off-label use and a safety issue has been identified as derived from such use, if this risk is not already an important identified or potential risk for the target population (GVP Module V Section V.B.5.8.), the specific risk should be included as an important potential risk. Whenever possible, its name should be specific.*
    - *For example, "severe bleeding [in off-label paediatric use]" should be used rather than the unspecific term "off-label use in children" if bleeding is not already included as an important identified or potential risk.*
    - *Other unspecific terms for which reference should be made to the particular risk, when possible, are "long-term use" or "medication error".*
- *A treatment has been proven effective only in adults (e.g. because the disease is very rare in children and, therefore, data in children could not be gathered and the medicinal product is likely to be ineffective or unsafe in this population). However, a high risk of off-label use in children related to the absence of effective and safe treatments in this patient population has been identified post-marketing. The potential safety harm to children resulted from the likely off-label use should be discussed in the RMP, a safety concern in the form of an important potential risk related to the specific safety concern should be considered, and paediatric post-marketing safety studies may therefore be a suitable pharmacovigilance activity, despite the restricted indication in adults.*
- *In animal studies, carcinogenicity was observed at clinically relevant exposures of a new medicinal product or the occurrence of secondary malignancy in humans after exposure is plausible based on the mechanistic properties of the medicinal product. However, the study observation period was too short or the study population was too small to establish a causal*

relation. "Secondary malignancies" should be considered to be added as an important potential risk.

- *Based on the characteristics and the mechanistic properties of a medicinal product, abuse of a medicinal product is possible and would lead to significant consequences such as addiction and death from overdosing. Nevertheless, abuse has not yet been observed. Risk from abuse/misuse should be listed as an important potential risk.*

Risk-benefit impact: *present the reasons for this classification, consider seriousness, frequency and severity as determinants; consider potential risks when, if confirmed in well-designed post-marketing studies, they would be classified as important identified risk due to the risk-benefit impact.*

<Missing information 1>:

Missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far (see GVP Module V section V.A.1). For example:

Use in subpopulations not studied (e.g. exclusion of a subpopulation from clinical studies) but within the approved indication: the absence of data itself does not automatically constitute a safety concern; instead, a scientific rationale for anticipating a different safety profile in the particular subpopulation /use is needed for the inclusion of that subpopulation as missing information, or that further data collection is warranted of another reason e.g.:

- *Patients with severe renal impairment were excluded from clinical trials, and the medicinal product is not contraindicated in this population, if the pharmacokinetic profile may be different in the excluded population (based on knowledge of the pharmacokinetic profile or the known mechanism of action) further data collection/ studies in such population are considered warranted. The safety concern should be classified as missing information "use in patients with renal impairment";*
- *A medicinal product is initially approved for treatment of adults and, subsequently, it is approved for treatment of the same disease in children based on a small clinical study in children (e.g. deferred paediatric development for selected age groups/indications). The approval is justified based on an extrapolation to the adult experience, both in terms of efficacy and safety. There are no specific safety concerns in children, as compared to the adult population. However, long-term safety data have not been studied at all in this population. In such case, 'long term safety in children' may be included as missing information. As limited data have been available at the time of marketing authorisation, a paediatric PASS should be considered as a suitable method of collecting post-approval safety data in children.*

In principle, the safety concern derived from the specific situations/data sources described in GVP Module V Section V.B.5.8. should be specified rather than using the unspecific term ("off-label use"; "medication error") if possible. For instance:

- *When a certain population has explicitly been excluded from the approved indication, but off-label use in this population is anticipated and a specific safety concern is associated with off-label use, then this specific safety issue should also be discussed in the RMP and considered to*

be added as a safety concern. e.g. cardiac safety in patients with prior significant cardiac history.

- *When there are potential risks related to cumulative or long-term exposure, e.g.: for a medicinal product, ototoxicity after long term use is a concern based on theoretical considerations, non-clinical data, and/or class effects, but long-term data is missing. There has been little or no long-term use of the medicine in clinical development. The particular concern of ototoxicity should be included in the RMP as a potential risk and long-term use should be added as missing information.*

Risk-benefit impact: *what are the reasons for this classification; what is the data that is still required to be gathered post-authorisation.*

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section applies to RMP updates after the granting of the marketing authorisation. When an important identified or potential risk or missing information is re-classified or removed, a justification should be provided in this RMP section, with appropriate reference to the safety data. The information included in this section may take the form of a statement describing a previous regulatory request, with a reference to the procedure where such request was formulated.

<<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/removal/addition to 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 marketing authorisation holder: Discuss briefly the level of scientific evidence that has led to this re-classification/removal, e.g. consider also seriousness and frequency as determinants (see examples in SVII.1). Further details on the safety concerns should be provided in section SVII.3, if applicable.

or <Previous regulatory request …>

Include procedure number and link/reference to the procedure submission where such request was formulated.

Further details on the safety concerns should be provided in section SVII.3, if applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

This section applies to all stages of the product life cycle.

SVII.3.1. Presentation of important identified risks and important potential risks

<Important Identified/Potential Risk>: *(using MedDRA terms when appropriate)*

Potential mechanisms:

Provide plausible biological mechanisms on how the administration of the medicinal product could lead to the event.

Evidence source(s) and strength of evidence:

Provide a brief summary of the main reasons for considering the risk as an important identified or important potential risk. Please consider that this text will be included verbatim in the RMP public summary.

Characterisation of the risk:

Describe the frequency, absolute risk, relative risk, severity, reversibility, long-term outcomes, and impact on quality of life, as applicable.

For frequency, state clearly:

- *Frequency parameter used e.g. incidence or reporting rates;*
- *Confidence intervals;*
- *Data source e.g. randomised clinical trial population, epidemiological study, post-marketing reporting data.*

For important identified risks incidence should be presented for the whole population and relevant subpopulation with differences discussed, if appropriate.

Risk factors and risk groups:

Describe patient factors, dose-related, at risk period, additive or synergistic factors. Please consider that this text will be included verbatim in the RMP public summary.

Preventability:

Provide data on predictability of a risk, factors that could increase the risk of an adverse reaction and how to minimise these, possibility of detection at an early stage which could mitigate seriousness.

When additional risk minimisation measures are proposed or are in place, make reference to the specific section in Part V where the measures are being described.

Impact on the risk-benefit balance of the product:

Describe the actual impact and the expected impact on the risk-benefit balance if the risk is further characterised (e.g. via pharmacovigilance plan and/or risk minimisation measures in place). It is expected that these new data confirms the presumed concerns (i.e. risk is minimised)?

Public health impact:

The purpose is to estimate how many events of a specific AE (safety concern) are to be expected in post-marketing. Where available, describe the absolute risk (incidence rate) in relation to the size of the target population and consequently actual number of individuals affected or describe the overall outcome expected on the population level.

SVII.3.2. Presentation of the missing information

Include only the missing information which has been selected to be part of the list of safety concerns.

<Missing information>: *(using MedDRA terms when appropriate or population name)*

Evidence source:

Describe any evidence that the safety profile is expected to be different from that in the general target population.

Select from following options:

Population in need of further characterisation:

If risks cannot be defined based on available evidence

Or

Anticipated risk/consequence of the missing information:

Describe the risk anticipated in the population not studied.

Describe the population followed up for further characterisation.

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns identified in previous Module SVII of Part II should be provided.

The summary should be provided for each medicinal product included in the RMP, if the list of safety concerns is different for different medicinal products.

This module is applicable for all initial marketing authorisation applications.

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

The Pharmacovigilance plan should provide details of pharmacovigilance activities/studies intended to identify and/or further characterise safety concerns and studies measuring the effectiveness of risk minimisation measures where such studies are required.

This part is applicable for all initial marketing authorisation applications.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance is the primary/minimum set of activities required to fulfil the legal requirements for pharmacovigilance contained in Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File describing these activities is not required to be repeated in the RMP. Signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all medicinal products but should not be discussed here.

For well characterised safety concerns, routine pharmacovigilance may be sufficient.

Part III.1 should only include a brief description of the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection (see examples in the GVP Module V, section V.B.6.1.).

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

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 4 of the RMP.

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 type of activity and not by safety concern.

III.2 Additional pharmacovigilance activities

The Applicant/Marketing authorisation holder should describe additional pharmacovigilance activities such as non-clinical, clinical or epidemiological (non-interventional or interventional) studies, and explain why they are needed. e.g.:

- *Long-term follow-up extensions of ongoing clinical trial(s);*
- *Cohort studies to provide additional characterisation of the long term safety of the medicinal product;*
- *Further effort to evaluate the missing data.*

For generic medicinal products, the pharmacovigilance plan will reflect their outstanding needs for pharmacovigilance investigations at the time of their approval.

Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification irrespective of whether the studies are to identify and characterise important risks/missing information, or to assess the effectiveness of additional risk minimisation activities using behavioural or safety outcome indicators.

Tabulated summary of on-going and completed pharmacovigilance study programme should be provided in Annex 2.

Protocols for studies in the pharmacovigilance plan should be provided in Annex 3 of the RMP until completion of the study and submission to the competent authorities of the final study report.

When any doubt exists about the need for additional pharmacovigilance activities, consultation with a competent authority should be considered. Further guidance on the conduct of post-authorisation safety studies (PASS) is provided in the GVP Module VIII.

For all safety studies imposed as condition of the marketing authorisation (category 1), as specific obligations in the context of a marketing authorisation under exceptional circumstances or conditional marketing authorisation (category 2), or required by the competent authority (category 3) complete the following summary. This should not be a duplication of the protocol synopsis, but it should be detailed enough to be able to inform what the study will add to further characterise the safety profile of the product. It should be also consistent with the study description provided in table III.3 and should include:

<PASS short name summary>

Study short name and title:

e.g. EPI-PM-006 - Medicinal Product observational cohort safety study in immunocompromised patients

Please consider that the text of the study title will be included verbatim in the RMP public summary.

Rationale and study objectives:

Indicate the rationale for conducting the study (include also all the safety concerns addressed).

Present briefly the study objectives.

Please consider that the text in this section will be included verbatim in the RMP public summary.

Study design:

State the study design. e.g. randomised clinical trial extension, observational chart-review, cohort study, self-controlled case series

Study population:

Present briefly the population included in the study, in line with the inclusion and exclusion criteria.

Milestones:

Include all requested milestones for reporting to the regulatory authorities (e.g. protocol submission, interim reports, and final report submission) as well as major milestones from study protocol (e.g. registration in the EU PAS register, start/end of data collection, interim progress reports, final study report completion, date of publication).

III.3 Summary Table of additional Pharmacovigilance activities

This section should be a complete overview of all on-going and planned categories 1-3 safety studies included in the Pharmacovigilance Plan, regardless of whether they were designed to assess the safety of the medicinal product, or the effectiveness of the risk minimisation measures.

Information on the study population should be part of the information provided in the study objectives as indicated in the example tabulation e.g. to evaluate the long term safety of adult/ paediatric/ adolescent/ elderly/ very elderly patients with Type 1 diabetes.

Clear milestones and due dates should be provided (e.g. submission of final study report by 31/01/2018). Submission of interim results or other intermediate milestones (e.g. submission of a draft protocol) is not expected unless explicitly requested by the competent authority; such request would need to be documented in the RMP and the relevant intermediate milestones/due dates added. Final report due dates should be provided for all studies included in the table below. This date should be in accordance with Annex IID/IIE conditions for studies category 1 and 2, respectively.

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

Table Part III.1: On-going and planned additional pharmacovigilance activities

Examples of activities are provided in green in the table, to guide on the level of the detail expected. Not all milestones are applicable for all studies, and not all products will have studies from all categories.

Study *(study short name, and title)* **Status** *(planned/on-going)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** *(required by regulators)*	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)*				
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* *Final report*	*31/01/2019* *31/12/2018*
Long-term safety registry (Study REG4321) *Planned*	*To evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus, using data from a long-term safety registry where all patients are followed for a minimum of 5 years,*	*- serious infections (including opportunistic infections and PML)* *- selected serious psychiatric events* *- malignancies (including non-melanoma skin cancer).*	*Protocol submission* *Final report*	*28/02/2017* *30/10/2023*
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				

Study *(study short name, and title)* **Status** *(planned/on-going)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** *(required by regulators)*	**Due dates**
Long term safety PASS – EPIOA005 *On-going*	*Primary* *• To further evaluate the long-term safety profile of <product> in the treatment of patients with <…> when used under conditions of routine clinical care* *Secondary* *• To further evaluate the long-term effectiveness of <…> in the treatment of patients with <…> when used under conditions of routine clinical care* *• To quantify discontinuation of treatment due to adverse events or due to lack of or loss of therapeutic response.* *• To further elucidate the risk of abnormal liver function tests and hepatitis*	*- Long term safety* *- Use in populations not studied in clinical trials: pregnancy and lactation, elderly, children under 14 years of age, hepatic impairment, renal impairment*	*Annual reports*	*To be submitted with annual re-assessments*
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
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 utilisation for <product>.*	*- Cardiac risk*	*Annual update*	*Progress reports on enrolment and intermediate analysis results will be provided yearly.*
			Final report	*31/03/2020*
Drug utilisation study for <product> DUS-01 *Planned*	*To document the real-life use of the product and to monitor off-label use.* *To measure the effectiveness of routine risk minimisation measures, e.g. the compliance with the SmPC recommendations on dose reduction in renal impaired patients.* *To measure the effectiveness of the educational materials, i.e. the off-label use in paediatric population.*	*- Safety in renal impaired patients* *-Off-label use in paediatric population*	*Final report*	*31/01/2019*
Post-approval safety surveillance program for lot-specific adverse events Q-450-E01 *Planned*	*To evaluate any potential change in the frequency of hypersensitivity, immunogenicity or lack of drug effect events.*	*Changes in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process*	*Final report*	*2 years following the expiry of the first released finished batch 31/01/2020*

Study *(study short name, and title)* **Status** *(planned/on-going)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** *(required by regulators)*	**Due dates**
Data collection from participation in the <Disease> registry *Planned*	*To monitor the treatment safety of <indication>*	*- Inhibitor development* *- Thromboembolic events* *- Serious allergic reactions or anaphylaxis*	*Regular updates*	*Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs, when available.*

Part IV: Plans for post-authorisation efficacy studies

*Include a list of the planned and on-going **imposed** post-authorisation efficacy studies, i.e. imposed by the competent authority as a condition of marketing authorisation or which are Specific Obligations in the context of conditional marketing authorisation or marketing authorisation under exceptional circumstances.*

Protocol(s) should be provided in Annex 5.

If not such studies are required, this part may be left empty.

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

Examples of activities are provided in green in the table, to guide on the level of the detail expected. Not all milestones are applicable for all studies. Submission of intermediate milestones imposed by the competent authority should be included. Final study report due dates should always be included in accordance with Annex II conditions.

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

Study *(study short name and title),* **Status** *(planned, on-going)*	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
Extension of clinical trial for <product>(SUMACI) *(on-going)*	*To examine the 5-year efficacy and safety of <product>, compared with reference treatment, in patients who received study treatment in the pivotal sponsored study for treatment of <…>.*	*Long term efficacy and safety*	*Final report*	*30/06/2022*
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

Study *(study short name and title),* **Status** *(planned, on-going)*	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
External natural history controlled, open-label interventional study to assess the efficacy and safety of <product> in the treatment of <indication>, including long-term treatment (CLINI-EXT-05) *On-going*	*To further investigate the benefits of <product> in the treatment of <…>,*	*Long-term efficacy*	*Protocol submission*	*28/02/2017*
			Interim reports	*To be submitted with annual re-assessment*
			Final report	*31/12/2022*
A global, prospective, non-interventional, observational study in the treatment of <indication> (AXAB-9001) *Ongoing*	*To provide a report of descriptive data on 1000 patients including 200 patients treated with <product>*	*Long term efficacy and safety*	*Final report*	*30/06/2019*

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

This part is applicable for all initial marketing authorisation applications.

Risk Minimisation Plan

For initial marketing authorisation applications for generic, hybrid medicinal products and fixed combination product with no new active substance, if the medicinal product does not have additional risk minimisation activities, the following statement may be sufficient and sections V.1 – V.3 may not be applicable:

<The safety information in the proposed product information is aligned to the reference medicinal product.>

However, if new important risks have been identified for the submitted product, the risk minimisation activities for such safety concerns should be presented in Part V, following the same requirements as for a full marketing authorisation application. If the originator medicinal product does have additional risk minimisation activities, a full Part V is required for these medicinal products.

Further guidance on risk minimisation measures can be found in GVP Module XVI and GVP Module XVI Addendum I – Educational materials.

V.1. Routine Risk Minimisation Measures

Include all safety concerns from Part II: Module SVIII.

This section may not be applicable for initial marketing authorisation applications for generic, hybrid medicinal products and fixed combination product with no new active substance, where the originator product does not have additional risk minimisation activities.

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.*
<Safety concern 2>	<None>

V.2. Additional Risk Minimisation Measures

This section should present the additional risk minimisation measures. The proposed draft key messages of additional risk minimisation activities should be provided in the RMP Annex 6.

For medicinal products approved non-centrally, in situations where the need for additional risk minimisation may vary across member states, the RMP can reflect that the need for (and content of) additional risk minimisation can be agreed at national level.

This section may not be applicable for initial marketing authorisation applications for generic, hybrid medicinal products and fixed combination medicinal product with no new active substance, where the originator medicinal product does not have additional risk minimisation activities.

Select from following options:

Statement that there is no need for additional risk minimisation activities

<Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.>

Or

<Additional risk minimisation 1>

Further extensive guidance on additional risk minimisation measures and on monitoring the effectiveness of risk minimisation activities is provided in GVP Module XVI, but examples of the materials most frequently used are included below:

Healthcare Professional and Patient/Carer Guide

The term guide can refer to any descriptive material that educates Healthcare Professional and/or patients/caregivers about specific risks, and/or their early symptoms, and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information. A guide may also aim to raise awareness about an on-going (imposed) registry/study, as well as about the general value of reporting adverse events. Terms such as 'brochure', 'leaflet' should be avoided and the term 'guide' should be used instead.

Healthcare Professional training material

In case of complex medicinal products, guides may be supplemented with training materials. They are commonly used to train Healthcare Professional when new complicated administration procedures (e.g. intra-vitreal injections, imaging diagnostics, ATMPs, etc.) are introduced or diagnostic products are first authorised, in order to minimise the potential risks associated with performing such procedures.

Prescriber checklist

Used to facilitate patient selection when initiating therapy or repeat prescription is issued, as appropriate. The checklist should remind prescribers of e.g. a restricted indication, contraindications, warnings and precautions needed for the use of a medicinal product particularly relating to important safety concerns in the SmPC and to facilitate the need for examination of specific aspects of the patient's health before initiating treatment and/or during continuous monitoring as appropriate.

Patient diary

It is generally requested to record information on the recommended treatment (e.g. date and/or outcome of specific tests needed) to facilitate regular monitoring of the patient's health status with respect to the medicinal product related safety concerns or particular signs and symptoms that can be discussed with the Healthcare Professionals. It is useful for the patient to read about precautions needed to minimise important risks.

Patient alert card

The aim of this tool should be to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information should be kept to the minimum necessary to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency. Ability to carry with ease (e.g. can be fitted in a wallet) should be a key feature of this tool.

Pregnancy prevention programmes

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a medicinal product by the biological father might have a negative effect on the pregnancy outcome. A PPP combines the use of educational tools with interventions to control appropriately access to the medicine. Therefore, the following elements should be considered individually and/or in combination in the development of a PPP.

• Educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimise this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraceptives; information included for the patient on how long to avoid pregnancy after treatment is stopped; information for when the male partner is treated;

• Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product;

• Prescription limited to a maximum of 30 days supply;

• Counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

Objectives:

Include objectives including a list of risks addressed.

Rationale for the additional risk minimisation activity:

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

Target audience and planned distribution path:

Include very brief summary of planned communication plan.

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

Specify how effectiveness will be measured and provide the criteria for judging success. Milestones for reporting should be included when effectiveness is evaluated using only routine pharmacovigilance activities.

<Removal of additional risk minimisation activities>

<Rationale for the removal:>

Include justification when an additional risk minimisation activity is proposed to be removed from the RMP.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Include all safety concerns from Part II: Module SVIII. Examples below are provided in green in the table, to guide on the level of detail expected. For clarity, a further summary of pharmacovigilance activities should also be included for clarity.

Although the title of the section makes reference to the risk minimisation activities, to facilitate the drafting and the publication of the RMP summary, as well as to have an overview of risk management activities in the RMP, the table also includes pharmacovigilance activities.

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

This section may not be applicable for initial marketing authorisation applications for generic, hybrid medicinal products and fixed combination product with no new active substance, where the originator medicinal product does not have additional risk minimisation activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
<Safety concern 1>	<Routine risk minimisation measures:> *Provide only reference to SmPC/PL section (do not copy the complete SmPC/PL wording) e.g.:* *<SmPC section 4.1 and 4.8>* *<SmPC section 4.4 where advice is given on monitoring the liver function>* *<PL section 2>* *<Pack size>* <Additional risk minimisation measures:> *e.g.* *<Healthcare Professional Guide>* *<Patient guide>* *<Surgeons' checklist>* *<Rehabilitation Manual>* <No risk minimisation measures>	*Include only a list of elements* <Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> *<AE follow-up form for adverse reaction>* <Additional pharmacovigilance activities:> *<Study short name>* <None>

Part VI: Summary of the risk management plan

A separate RMP Part VI should be provided for each product in the RMP. As it is a stand-alone document, do not include any references to other parts of eCTD dossier or other medicinal products published RMP summaries.

This section should be submitted for all initial marketing authorisation applications and all post-authorisation RMP updates.

Summary of risk management plan for <invented name> (<INN>)

This summary should be updated to reflect any important change to the RMP[15] and be consistent with other RMP parts/modules.

This is a summary of the risk management plan (RMP) for <invented name>. The RMP details important risks of <invented name>, <how these risks can be minimised>, and how more information will be obtained about <invented name>'s risks and uncertainties (missing information).

<Invented name>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <invented name> should be used.

For centrally authorised medicinal product only:

<This summary of the RMP for <invented name> should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR)>.

Important new concerns or changes to the current ones will be included in updates of <invented name>'s RMP.

I. The medicine and what it is used for

<Invented name> is authorised for <indication outline *– from Table Part I.1 – Indication(s) in the EEA*> (see SmPC for the full indication). It contains <INN> as the active substance and it is given by <route of administration *– from Table Part I.1 "pharmaceutical form(s) and strengths"*>.

For centrally authorised medicinal product only:

<Further information about the evaluation of <invented name>'s benefits can be found in <invented name>'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*Pre-authorisation RMP (this line should be only edited by EMA):* link to the EPAR

[15] Changes are considered important if they relate to the following: new safety concerns or important changes/removal to a known safety concerns, major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies), any 'additional risk minimisation measure' which is added or removed, routine risk minimisation activities recommending specific clinical measures to address the risk.

summary landing page. *Post-authorisation RMP (this line should be edited by the Applicant/MAH):* link to product's EPAR summary landing page on the EMA webpage.>

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of <invented name>, together with measures to minimise such risks and the proposed studies for learning more about <invented name>'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

Include the sentence below, if the RMP (Part V.2) includes additional risk minimisation measures:

<In the case of <invented name>, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below>.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed <, including PSUR assessment - *include PSUR statement only if product has PSUR requirements*> so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

Include the sentence below, if the RMP does contain missing information in the summary of safety concerns:

<If important information that may affect the safe use of <invented name> is not yet available, it is listed under 'missing information' below>.

II.A List of important risks and missing information

Important risks of <invented name> are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely <administered> <taken>. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <invented name>. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information *(from Part II: Module SVIII)*	
Important identified risks	<>
Important potential risks	<>
Missing information	<>

II.B Summary of important risks

If Module SVII is not applicable (see Part II Module SVII requirements) and the reference medicinal product does not have additional risk minimisation activities and no additional pharmacovigilance activities are requested, include only this statement:

<The safety information in the proposed Product Information is aligned to the reference medicinal product.>

If Module SVII is applicable (see Part II Module SVII requirements) or the reference medicinal product has additional risk minimisation activities or additional pharmacovigilance activities, provide the following information for each risk/ missing information:

- *Module SVII is applicable:*

<Important <identified> <potential> risk > or <Missing information>	
Evidence for linking the risk to the medicine *Delete this row for tables summarising missing information*	*Use text from RMP Part II SVII.3.1 under 'Evidence source(s) and strength of evidence' or the corresponding SVII "Justification of <new safety concerns> <and/or reclassification> with a submission of this RMP in comparison with the reference medicinal product published on <EMA/national competent authority/CMDh> website" if SVII.3.1. is not applicable*
Risk factors and risk groups *Delete this row for tables summarising missing information*	*Use text from RMP Part II SVII.3.1 under "Risk factors and risk groups"* <Not applicable> *if RMP Part II SVII.3.1 is not applicable*
Risk minimisation measures	<Routine risk minimisation measures> *Use text from table Part V.3.* <Additional risk minimisation measures> *Use text from table Part V.3.* <No risk minimisation measures>
Additional pharmacovigilance activities *This row should be removed in case there are no additional pharmacovigilance activities*	Additional pharmacovigilance activities: <Short study name> *Use study short name from table Part V.3.* See section II.C of this summary for an overview of the post-authorisation development plan.

- *Module SVII is not applicable but there are additional risk minimisation activities or additional pharmacovigilance activities:*

<Important <identified> <potential> risk 2> or <Missing information> *Fill this table for each risk that have corresponding additional risk minimisation activities or additional pharmacovigilance activities*	
Risk minimisation measures *This row should be removed if RMP Part V.3 is not applicable*	<Routine risk minimisation measures> *Use text from table Part V.3* <Additional risk minimisation measures> *Use text from table Part V.3.*
Additional pharmacovigilance activities *This row should be removed in case there are no additional pharmacovigilance activities*	Additional pharmacovigilance activities: <Short study name> *Use study short name from table Part V.3 or from Table Part III.2 if Part V.3 is not applicable.* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

<The following studies are conditions of the marketing authorisation:>

Include studies category 1 and 2 from Table Part III.1: On-going and planned additional pharmacovigilance activities.

Include all studies from Table Part IV.1: Planned and on-going post-authorisation efficacy studies which are a condition of the marketing authorisation or which are a specific obligation.

<**Study short name**> *Include text from Part III.2 and/or Part IV.*

Purpose of the study: *Include text from Part III.2 'Rationale and study objectives' and/or Part IV 'Summary of objectives'.*

<There are no studies which are conditions of the marketing authorisation or specific obligation of <invented name>.>

II.C.2 Other studies in post-authorisation development plan

Include category 3 studies from Table Part III.3: On-going and planned additional pharmacovigilance activities.

<**Study short name**> *Include text from Part III.2.*

Purpose of the study: *Include text from Part III.2 'Rationale and study objectives'.*

<There are no studies required for <invented name>.>

Part VII: Annexes

For generic (Article 10 (1)) and hybrid (Article 10 (3)) medicinal products, the same requirements as for initial marketing authorisation application for a new active substance apply. For annexes 4 and 6, materials should be kept as similar as possible with the originator product in order to deliver a consistent message. Therefore, marketing authorisation holders are strongly encouraged to share the content of their material(s) upon request from other marketing authorisation holders.

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Include TOC of Annexes (it is predefined and not considered as confidential information).

Annex 1 – EudraVigilance Interface

Annex 1 of the RMP is not required to be submitted in eCTD; the electronic file should be submitted in accordance to GVP Module V section V.C.2 and the guidance on the website[16].

Leave Annex 1 empty.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

*List **all** studies included in the Pharmacovigilance Plan (current or in previously approved RMP versions).*

Table 1 Annex II: Planned and on-going studies

Study *Include study short name, title and category number*	**Summary of objectives**	**Safety concerns addressed**	**Protocol link Milestones** *Include link or reference to full protocol (included in RMP Annex 3 or eCTD).* *Include planned submission dates of interim and final study report requested by the Competent Authorities.*
e.g.: *LE observational cohort safety study (study LE123)* *Category 1*	*e.g. 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.*	*e.g.:* *- 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).*	*Link to protocol* *Interim results:31 December 2016* *Final study report submission: 15 July 2020*

Table 2 Annex II: Completed studies

16 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000683.jsp&mid=WC0b01ac058067a113

Study *Include study short name, title and category number*	**Summary of objectives**	**Safety concerns addressed**	**Date of Final Study Report submission** **Link to report** *Include date of report submission or state the reason for not submitting the results.* *Include link or reference to full Final Study report (included in eCTD).*
e.g.: *An open-label, multicentre evaluation of the long-term safety and efficacy of drug A in the prevention and treatment of bleeding episodes in previously untreated patients with acquired haemophilia A* *A123* *Category 2*	*e.g. To evaluate the long-term safety in subjects with acquired haemophilia A*	*e.g.* *- Long-term safety* *- Safety profile in patients ≥ 75 years*	*27 May 2015* *Link to final study report*

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 3 should include protocols of imposed studies (categories 1 and 2) and protocols for those required studies (category 3). Protocols of studies not imposed or not required should not be included.

This annex may include the electronic links or references to other modules of the eCTD dossier where the protocols are included, instead of the full protocol documents.

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Include ToC

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

If protocols have been requested to be submitted for review by the competent authority, and the marketing authorisation holder choses to submit for assessment a study protocol within the same procedure as the RMP submission, part A should include this protocol; alternatively the protocol might be reviewed in a stand-alone procedure, and once agreed, included in the RMP annex 3 – part C.

When a protocol not yet approved is submitted to address a request for supplementary information, a track changes version of any updated protocol and an executive summary of how outstanding points have been addressed should be always submitted (e.g. in the cover letter of the procedure).

<Full protocols or links/references to eCTD documents>

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

If protocol amendments have been requested to be submitted for review by the competent authority, and the marketing authorisation holder choses to submit for assessment the study protocol amendment within the same procedure as the RMP submission, part B should include the

updated protocol; alternatively the protocol amendment might be reviewed in a stand-alone procedure, and once agreed, included in the RMP annex 3 – part C.

Once approved, protocols from parts A or B should be moved to part C, with the next warranted RMP update.

<Full protocols or links/references to eCTD documents>

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

This section should include:

- *The final approved protocols for studies included in the Pharmacovigilance Plan (current or in previously approved RMP versions). They should be accompanied by the name of the procedure when the protocol was approved and date of the procedure outcome.*
- *The protocols not reviewed or not approved for category 3 studies, for information only.*

Protocols of completed studies should be removed from this annex once the final study reports are submitted to the competent authority for assessment.

Approved protocols:

<Procedure number where the protocol was approved>

<Full protocols or links/references to eCTD documents>

Final protocols not reviewed or not approved:

<Full protocols or links/references to eCTD documents>

Annex 4 - Specific adverse drug reaction follow-up forms

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Follow-up forms

Provide the specific adverse drug reaction follow-up forms in full.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

This section should include links or references to other parts of the eCTD dossier, where the protocol for an imposed efficacy study was submitted. This information is meant to facilitate the assessment by maintaining an overview of the post-authorisation efficacy and safety development plans.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

<Draft/approved> key messages of the additional risk minimisation measures

Example: Key messages are included before initial approval of the product (D1- D181) for review and assessment. For Centrally Authorised Products, the PRAC, CHMP (or CAT, if applicable) and EMA will review and agree a final version that will be included in Annex II of the marketing authorisation. If the product requires a revision of the key messages post-marketing, an amended set of key messages can be proposed for assessment in Annex 6 by the Marketing authorisation holder (tracked changes).

In exceptional situations, it may be possible to tailor the key elements within the RMP to specific national situations or treatment behaviours/guidelines, i.e. some key elements may be unique for some EU Member States. However, it should be kept in mind that key elements considered applicable for all Member States will be included in Annex II of the marketing authorisation (for centrally authorised products) or as a condition of the marketing authorisation for DCP/MRP and purely national products.

Examples of key messages for different types of additional risk minimisation materials:

Physician educational material:

- <The Summary of Product Characteristics>

In addition to the Summary of Product Characteristics select all tools that apply:

- <Guide for healthcare professionals>
- <Healthcare professionals training material>
- <Prescriber checklist>
- <Patient alert card>

Based on the choice on the above listing, select all relevant elements and edit as required.

- **Guide for healthcare professionals**:
  - <Relevant information of the safety concern(s) addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)>
  - <Details of the population at higher risk for the safety concern addressed by the aRMM (e.g. contraindications, risk factors, increased risk by interactions with certain medicine)>
  - <Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (e.g. what to do, what not do, and who is most likely to be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)>
  - <Key message to convey in patients counselling >
  - <Instructions on how to handle possible adverse events>
  - <Information about the <name of> <study> <registry> and the importance of contributing to such a study>
  - <Remarks on the importance of reporting on specific adverse reactions, namely: < adverse reaction 1, adverse reaction 2 etc…>
  - <Other to be specified>
- **Healthcare professionals training material**:
  - <Information on <product name>, including the approved indication according to the SmPC>
  - <Detailed description of the administration procedures of <PRODUCT NAME>>
  - <Patient's preparation for the procedure and subsequent monitoring>

- <Management of early signs and symptoms of selected safety concerns, namely: safety concern 1, safety concern 2, etc.>
- <Other to be specified>

For diagnostic products, select additional information:

- <Limitations of <PRODUCT NAME> use, interpretation errors, safety information and the results of clinical trials informing on the diagnostic use of <PRODUCT NAME>>
- <Review of the imaging reading criteria, including method of image review, criteria for interpretation, and images demonstrating the binary read methodology>
- <Demonstration cases with correct imaging interpretation by an experienced reader and a number of clearly positive and negative cases as well as less clear-cut cases>

- **Prescriber checklist**:
  - <Lists of tests to be conducted for the initial screening of the patient>
  - <Vaccination/treatment course to be completed/withdrawn before/after treatment>
  - <Premedication, general health, and pregnancy and contraception checks immediately before/during/after treatment>
  - <Monitoring activities during treatment and for X years after last treatment>
  - <A specific reference to the fact that the patient has been informed and understands the <potential> <teratogenic> risks of <specify risk(s)> and the measures to minimise them>
  - <Other to be specified>
- **Patient alert card**:
  - <A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using <PRODUCT NAME>>
  - That <PRODUCT NAME> treatment may increase the <potential> risk of: <Risk 1, Risk2, etc.>
  - Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
  - Contact details of the <PRODUCT NAME> prescriber

The patient information pack:

- Patient information leaflet

In addition to the patient information leaflet select all that applies:

- <A patient/carer guide>
- <A patient diary>

Based on the choice on the above listing, select all relevant elements and edit as required. The suggested key elements are not strictly supposed to be used only for the related specific tool (see example below):

- **Patient/carer guide**:
  - <A description of the <potential> <teratogenic> risks(s) associated with the use of <PRODUCT NAME> namely: <Risk 1, Risk2, etc.>
  - <A description of the correct use of <product name> and the <potential> risks associated with its use, namely: <Risk 1, Risk2, etc.>
  - <Detailed description of the modalities used for the self-administration of <PRODUCT NAME>>
  - <A description of the <early> sign and symptoms of the <potential> risk of <specify risk(s)>
  - <A description of the best course of action if sign and symptoms of those risks present themselves (e.g. How to reach your doctors)>
  - <Recommendations for the planning of the monitoring schedule>
  - <Information about the <name of> <study> <registry>>
  - <Remarks on the importance of reporting on specific adverse reactions, namely: < adverse reaction 1, adverse reaction 2 etc…>
  - <Other to be specified>
- **Patient diary**:
  - <A record on the recommended treatment <date> <outcome of specific test(s)> to facilitate regular monitoring of the patient´s health status to product related <Risk 1, Risk2, etc.> or <particular symptoms that can be discussed with the Physician etc.>>
  - <A description of precaution(s) needed to minimise <Risk 1, Risk2, etc.> associated with the use of <PRODUCT NAME>>

For pregnancy-related risks, select additional information:

- <Recommendation not to take <PRODUCT NAME> in case of pregnancy>
- <For women of child bearing potential recommendation to use effective contraception methods>
- <Recommendation for regular pregnancy testing>

Annex 7 - Other supporting data (including referenced material)

Only key literature referenced in the RMP should be included in the format of electronic links or references if already included in other modules of the dossier.

Annex 8 – Summary of changes to the risk management plan over time

A list of all significant changes to the Risk Management Plan over time

Version	**Approval date** **Procedure**	**Change**
<e.g.	<At the time of	*Add high level description of major changes:*

7.0>	authorisation> <procedure number> dd/mm/yyyy	<Safety concerns> *Important Identified/Potential Risk/Missing information 1: Added/ Removed/ Reclassified* <Pharmacovigilance Plan> *Study 1:* • *Added as a new safety concern <Important identified risk 1> has been identified and need to be further characterised* • *Due date postponed due to difficulties with patient recruitment* • *Removed as study has been completed and obligation has been fulfilled* <Post-authorisation efficacy plan> <Risk minimisation measures> *Additional risk minimisation 1:* • *Added/ Modified to increase the patient´s awareness on the signs and symptoms relevant to the early recognition of increased plasma levels in patients with specific polymorphism* • *Added to inform the healthcare professionals about the new available information regarding heart failure* <Annexes> • *Annex 4: Specific adverse drug reaction follow up forms 1 added*