

Guidance on the Early Access to Medicines Scheme (EAMS) full risk management plan (RMP)

*All EAMS applications require an EAMS RMP. The template below is for a full EAMS RMP and should be used in the case that the applicant does not have a marketing authorisation for the medicinal product concerned.*

*An abridged version of the EAMS RMP can be used in the case where there is an RMP approved for an authorized product in the UK that is relevant to the use through EAMS. This would usually apply for an authorized drug for which the important safety concerns can be expected to be the same as those in its use through EAMS.*

*All sections of the template should be completed. Guidance is provided in green text.*

*In brief, the structure of the EAMS RMP is as follows*

*Part I: Product overview*

*Part II: Safety specification – this section largely is in line with the EU RMP rev 2 template*

*Part III: Pharmacovigilance Plan – this section is specific for EAMS*

*Part IV: Plans for further efficacy studies - this section is largely in line with the EU RMP rev 2 template*

*Part V: Risk minimization plan – this section is largely in line with the EU RMP rev 2 template*

*Part VI: Annexes – these are largely consistent with the EU RMP rev 2 template*

*Blue highlighting – indicates a notable difference compared with the EU RMP rev 2*

*In addition to the green text in the template below, please refer to MHRA guidance on pharmacovigilance procedures[[1]](#footnote-2), GVP V, the EU RMP rev 2 template and the* *[Guidance on applying to the EAMS](https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams) for further reference.*

Early Access to Medicines Scheme (EAMS) full risk management plan (RMP) template (version 2.1)

| Active substance(s) (INN or common name): |  |
| --- | --- |
| Pharmaco-therapeutic group  (ATC Code): |  |
| Name of Opinion Holder or Applicant: |  |
| Medicinal product(s) to which this RMP refers: | *Indicate total number of products to which the RMP refers.* |

<Enter a version no>

<Enter a date>

Data lock point for this RMP Version number

<Enter a date>

Date of final sign off

Version number of last agreed RMP:

Version number

<Enter a version no>

QPPV Name

QPPV Signature

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Part I: Product(s) Overview

Administrative information on the RMP

|  |  |
| --- | --- |
| **Brief description of the product including:**   * chemical class * summary of mode of action * important information about its composition *(e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines* |  |
| **Indication(s) under EAMS**  Current (if applicable)  Proposed (if applicable) |  |
|  |
| **Posology and route of administration under EAMS**  Current (if applicable)  Proposed (if applicable) |  |
|  |
| **Pharmaceutical form(s) and strengths**  Current (if applicable)  Proposed (if applicable) |  |
|  |

Part II: Safety specification

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

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

| Key Safety findings (from non- clinical studies) | Relevance to human usage |
| --- | --- |
| Toxicity including:   * key issues identified from acute or repeat-dose toxicity studies * reproductive/developmental toxicity * genotoxicity * carcinogenicity |  |
| Safety pharmacology:   * cardiovascular (including potential for QT interval prolongation) * nervous system * etc. |  |
| Other toxicity-related information or data |  |

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).

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.

Part II: Module SIII - Clinical trial exposure

SIII.1 Duration of exposure

*The following tables should be provided for each indication with a summary table showing total exposure.*

*Provide each table, where available, based on exposed (to medicinal product of interest) persons in all clinical trial populations*

Data should be pooled and **NOT** shown per trial unless there are clear, justified reasons (to be provided) why some data should not be amalgamated.

If there is only one indication, totals can be provided. Otherwise the table should be stratified by indication.

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

| **Table SIII.2: Age group and gender**  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 |  |  |  |  |

When providing data by age group, the age group should be relevant to the target population. Artificial categories such as <65, >65 should be avoided. Paediatric data should be divided by categories (e.g. ICH-E11). Similarly, the data on older people should be stratified into categories such as 65-74, 75-84 and 85+ years. For teratogenic drugs, stratification into age categories related to childbearing potential might be appropriate for the female population.

If the RMP includes more than one medicinal product, the total population table should be provided for each product as well as a combined table.

| Table SIII.3: Dose | | |
| --- | --- | --- |
| Dose of exposure | Persons | Person time |
| Dose level 1 |  |  |
| Dose level 2 etc. |  |  |
| Total |  |  |

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

|  |  |  |
| --- | --- | --- |
| **Table SIII.4: Ethnic origin** | Patients | Person time |
| <Indication 1> |  |  |
| *Ethnic origin 1* |  |  |
| *Ethnic origin 2 etc.* |  |  |
| Total |  |  |

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.

SIV.1 Effect of exclusion criteria in the clinical trial development plan

Discuss the important exclusion criteria across the clinical trial 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

This section aims to present the size of the safety database in each of the populations that are under-represented.

Some populations are often excluded or under-represented in clinical trials. For each of the lines 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.*  *Do not include clinical trials inclusion/exclusion criteria.* |
| 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

**Include module SV ONLY for new active substances which have been previously been authorised or made available to patients on a compassionate/named-patient use basis anywhere in the world. Otherwise, this RMP module can be omitted.**

SV.1 Estimated post-authorisation exposure

Summarise the **estimated** exposure (e.g. packs or person-years treatment). Explain what method has been used to calculate estimated exposure.

SV.2 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

List any cumulative significant regulatory action (including those initiated by the MAH in any market in relation to a safety concern). Significant regulatory action would include a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation.

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

Potential for misuse for illegal purposes

Discuss the potential for potential for misuse, e.g. as a recreational drug or facilitating assault etc. If appropriate 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.

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 treatment protocol, 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 and safety concerns related to a specific formulation or route of administration.*

*Exceptionally, if agreed with the MHRA 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 positive scientific opinion (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.*

***With regards to Advanced therapy medicinal products (ATMP)*** *the applicant should adapt the risk management plans of ATMP, considering and discussing the anticipated post-opinion follow-up needs, focusing on particularities of these medicinal products. The specific RMP content requirements for ATMP should be discussed with the MHRA before the submission. Further guidance on the safety and efficacy follow-up and risk management requirements for ATMP is provided on the European Medicines Agency website[[2]](#footnote-3). See the Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products[[3]](#footnote-4) for risks to be considered in drafting the safety specification.*

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

*This section is expected to be submitted only for initial applications, “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 already 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 reactionreporting, 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, either routine or additional.*

**<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 positive scientific opinion. 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 opinion 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. Data should be provided considering all possible sources, e.g. clinical trials from the current application; literature, pharmacovigilance data, etc. Do not cross reference other applications.

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

**<Important Identified/Potential Risk>:** *(using MedDRA terms when appropriate. Generally, only one MedDRA PT or SMQ is expected. Use verbatim if no MedDRA term adequately captures the given term. This list should not include the extensive list of PTs/LLTs used for MAH signal detection)*

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.*

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-opinion. 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. Generally, only one MedDRA PT or SMQ is expected. Use verbatim if no MedDRA term adequately captures the given term. This list is not meant to refer to the list of terms to be used when querying the MAH database)*

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 should be provided of each of the safety concerns identified in previous Modules of Part II.

This module is applicable for all initial 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

*The Pharmacovigilance plan (PhV Plan) provides details of pharmacovigilance activities which are intended to identify and/or characterise safety concerns with a focus on use of the product under EAMS. What is required will depend upon the nature of the medicine, the target population, the number of safety concerns and where the medicine is in its life-cycle. A PhV Plan may also include details of studies to measure the effectiveness of risk minimisation measures for important measures where a formal study is required.*

*For products with a positive Opinion through EAMS, a means of proactive safety data collection, eg in the form of a registry, will be required. For further information on the registry requirements, please see the* *published guidance for applicants for the Early Access to Medicines Scheme (EAMS):* [*https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams*](https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams)*.*

*Depending upon the safety concerns, and areas to be investigated, a PhV Plan may include other types of epidemiological (non-interventional) studies (such as cohort, case control, drug utilisation etc.) but may also include interventional studies or more rarely pre-clinical activities (such as PK/PD, clinical trials, in vivo or in vitro studies). Further information on post authorisation safety studies is given in GVP Module VIII.*

III.1 Routine pharmacovigilance activities

Include a statement to describe the routine pharmacovigilance activities. This should confirm that a PSMF is in place and that adverse events/adverse drug reaction reports will be managed and reported in line with the Good Vigilance Practice Module VI, MHRA guidance on the exceptions and modifications to the EU guidance on GVP[[4]](#footnote-5) and the requirements on reporting for EAMS. as described in the published guidance (<https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams#scientific-opinion>). The following statements should be included as applicable

<A pharmacovigilance system as described in the pharmacovigilance system master file is in place to support the pharmacovigilance tasks in relation to the product(s) concerned>

For an EAMS product with nationally licensed indication(s) in the UK (including in Great Britain and/or Northern Ireland):

<As per the Human Medicines Regulations 2012 as amended (HMR), regulation 188(1), all serious suspected adverse drug reactions (ADRs) are reported to MHRA within 15 calendar days of receipt and all non-serious suspected ADRs that occur in the UK are reported to MHRA within 90 calendar days of receipt. This includes suspected ADRs that arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.>

For an EAMS product with no nationally licensed indication(s) in UK:

<As per HMR regulation 170(3), all serious suspected ADRs are reported to MHRA within 15 calendar days of receipt>

*Additional requirements for reporting may be necessary:*

<The following additional pharmacovigilance reporting requirements apply:>

* <All suspected ADRs with a fatal outcome are reported to the MHRA within 7 calendar days of receipt, further information to be provided within 8 days>
* <All non-serious suspected ADRs are reported to MHRA within 90 calendar days of receipt>
* <other>

*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.).*

EAMS-specific forms for collection of adverse events should be provided in annex 3 as part of the pharmacovigilance protocol (see Module III.3).

*Where specific adverse reaction follow-up questions are used, their purpose and a description of the questionnaires used should be provided. The forms should be provided in Annex 4 of the RMP*

**III.1.1 Periodic update reporting**

Describe the timelines and frequency of periodic update reports.

Periodic reports should usually be submitted on a 3-monthly basis for the first year after positive scientific opinion. A one month period for preparation of the report is permitted, ie the first periodic report would have a data lock point at 3 months post-opinion and be submitted within 4 months post-opinion. A final periodic report is required following scientific opinion expiry and is to be submitted within 1 month after EAMS expiry.

For products that have had a positive EAMS opinion for 1 year or more, submission of periodic reports on a less frequent basis (e.g. 6-monthly) may be considered.

III.2 Additional pharmacovigilance activities

The plans for active pharmacovigilance for use of the product under EAMS, such as operation of a registry should be described here and the protocol provided in Annex 3.

*The Applicant should describe any other additional pharmacovigilance activities relevant to use of the product under EAMS, 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.*

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.

A tabulated summary of on-going and completed pharmacovigilance studies should be provided in Annex 2.

Protocols for the registry and any other studies in the pharmacovigilance plan should be provided in Annex 3 of the RMP until completion of the study and submission to the MHRA of the final study report.

When any doubt exists about the need for additional pharmacovigilance activities, consultation with MHRA should be considered and please also refer to the [Guidance on applying to the EAMS](https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams). Further guidance on the conduct of post-authorisation safety studies (PASS) is provided in the GVP Module VIII.

.

III.3 Table of on-going and planned additional PhV activities

This section should be a complete overview of all on-going and planned safety studies relevant to use of the medicinal product under EAMS and 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). Final report due dates (and interim report due dates where appropriate) should be provided for all studies included in the table below.

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

Note: Regardless of other milestones, EAMS Opinion Holders are expected to provide updates on findings from registries/studies within the Periodic Reports and to provide an annual report with each EAMS renewal application.

1. On-going and planned additional pharmacovigilance activities

| Study/activity type, title; status (planned, on-going) | Objectives | Safety concerns addressed | **Milestones** (mandatory) | Due date (mandatory) |
| --- | --- | --- | --- | --- |
| 1. <E.g. CRUCIAL  Cancer Registry at University College IdAho Liver unit  (non- interventional cohort);  *<On-going*> | <E.g. To investigate long term survival, time to progression> | <E.g.   * Bradycardia * Thrombosis * Leukopenia> | Protocol submission1 | DD/MM/YYYY |
| Final report | DD/MM/YYYY |
| Observational evaluation of safety of <product> in children and adolescent with high risk conditions  *<Planned*> | To investigate the safety of <product> in high risk paediatric patients |  | Protocol submission1 | DD/MM/YYYY |
| Annual report | DD/MM/YYYY |

Part IV: Plans for further efficacy studies

IV.1 Summary of Post-opinion efficacy development plan

The purpose of this section is to have an overview of the planned and on-going efficacy studies. The results of the efficacy studies are also expected to contain safety data and might have an impact on the safety profile of the product(s).

A synopsis of the protocol(s) of any efficacy or effectiveness studies required by MHRA should be provided in Annex 5.

1. Planned and on-going post-opinion efficacy or required effectiveness studies

| **Study (type and study number), status** (planned, on-going) | **Objectives** | **Efficacy uncertainties addressed** | **Milestone(s)** | **Due Date(s), if applicable (e.g. for studies required by MHRA)** |
| --- | --- | --- | --- | --- |
| <E.g. missing pivotal clinical trial;  *On-going*> |  |  | <E.g. Final report> | <DD/MM/YYYY> |
| <E.g. 5 year efficacy follow-up in cancer as a standard condition;  *On-going*> |  |  | <E.g. Final report> | <DD/MM/YYYY> |

Part V: Risk minimisation measures

Any additional risk minimisation measure should be described in Table V.1. For each safety concern identified in module SVIII “summary of the safety specification” a summary of any routine and additional risk minimisation measures should be provided. Where none are proposed, then “none proposed” should be entered against the safety concern.

Further guidance on additional risk minimisation measures can be found in GVP Module XVI.

V.1 Summary table of risk minimisation measures

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
| --- | --- | --- |
|  | Only reference to the general information included in the treatment protocol is needed here (i.e. specific wording is not needed) | (where applicable)  listing in line with section V.2 |

V.2 Details of Additional risk minimisation measures (if applicable)

*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.*

*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 Treatment Protocols. A guide may also aim to raise awareness about an on-going (required) 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 made available, 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.*

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |

Part VI: Annexes

Annex 1 – EudraVigilance Interface

Not required

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)* | *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

| 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* | *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 studies in the pharmacovigilance plan. A description of the proactive safety data collection (i.e. registry) for use of the product under EAMS should be included here.*

*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.*

*A table of contents should be provided.*

Annex 4 - Specific adverse drug reaction follow-up forms

**Table of contents**

**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 a required efficacy or effectiveness 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**

*Key messages are included before grant of positive scientific opinion for review and assessment. Final versions must be agreed with the MHRA before the product is made available to patients via EAMS.*

*If the product requires a revision of the key messages post-opinion, an amended set of key messages can be proposed for assessment in Annex 6 by the Marketing authorisation holder (tracked changes).*

Prior to the <launch><use> of <PRODUCT NAME> via EAMS the Opinion Holder must agree about the content and format of the <educational> <controlled access> <pregnancy prevention> <other> programme, including communication media, distribution modalities, and any other aspects of the programme, with the MHRA.

The <educational> <controlled access> <pregnancy prevention> <controlled distribution> <other> programme is aimed at *<describe main objectives of programme>*

The Opinion Holder shall ensure that all <healthcare professionals> <and> <patients/carers> who are expected to <prescribe> <dispense><use> <PRODUCT NAME> have access to/are provided with the following educational <package> <message to be disseminated through professional bodies>:

* <Physician educational material>
* <Patient information pack>
* <Other *(if any other audience is targeted it should clearly described)>*

**Physician educational material**:

* <The treatment protocol – information for healthcare professionals>

*In addition to the Treatment Protocol 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**:

* Treatment protocol – information for patients

*In addition to the Treatment Protocol, 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. 7.0> | <At the time of positive opinion>  <procedure number> dd/mm/yyyy | *Add high level description of major changes:*  <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* |

1. <https://www.gov.uk/government/publications/guidance-on-pharmacovigilance-procedures/guidance-on-pharmacovigilance-procedures>; <https://www.gov.uk/government/publications/exceptions-and-modifications-to-the-eu-guidance-on-good-pharmacovigilance-practices-that-will-apply-to-uk-mahs-and-the-mhra> [↑](#footnote-ref-2)
2. See [www.ema.europa.eu](http://www.ema.europa.eu); further ATMP-specific guidance is being developed [↑](#footnote-ref-3)
3. EMEA/149995/2008; available on EMA website <http://www.ema.europa.eu> [↑](#footnote-ref-4)
4. https://www.gov.uk/government/publications/exceptions-and-modifications-to-the-eu-guidance-on-good-pharmacovigilance-practices-that-will-apply-to-uk-mahs-and-the-mhra [↑](#footnote-ref-5)