EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2013
EMA/465932/2013 Rev.1[1]
Patient Health Protection

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

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorisation Holder or Applicant:	
Number of medicinal products to which this RMP refers:	Choose one of the following: • 1 • 2 • 3 • 4 • 5 • 6
Product(s) concerned (brand name(s)):	

Data lock point for this RMP	<Enter a date>	Version number	<Enter a version no>
Date of final sign off	<Enter a date>		

[1] Please note that under section VI.1.4 Summary table of Risk Minimisation Measures "Copy table from Part V: 5.2" should have read "Copy table from Part V: V.3"

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Part I: Product(s) Overview

Administrative information on the RMP

Part	**Module / annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted / or Not Applicable**
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	<Enter a date>	
	SII Non-clinical part of the safety specification	<Enter a date>	
	SIII Clinical trial exposure	<Enter a date>	
	SIV Populations not studied in clinical trials	<Enter a date>	
	SV Post-authorisation experience	<Enter a date>	
	SVI Additional EU requirements for the safety specification	<Enter a date>	
	SVII Identified and potential risks	<Enter a date>	
	SVIII Summary of the safety concerns	<Enter a date>	
Part III Pharmacovigilance Plan		<Enter a date>	
Part IV Plan for post-authorisation efficacy studies		<Enter a date>	
Part V Risk Minimisation Measures		<Enter a date>	
Part VI Summary of RMP		<Enter a date>	
Part VII	ANNEX 2	<Enter a date>	

Part	Module / annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted / or Not Applicable
Annexes	Current or proposed SmPC/PIL		
	ANNEX 3 Worldwide marketing status by country	<Enter a date>	
	ANNEX 4 Synopsis of clinical trial programme	<Enter a date>	
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	<Enter a date>	
	ANNEX 6 Protocols for proposed and on-going studies in Part III	<Enter a date>	
	ANNEX 7 Specific adverse event follow-up forms	<Enter a date>	
	ANNEX 8 Protocols for studies in Part IV	<Enter a date>	
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	<Enter a date>	
	ANNEX 10 Details of proposed additional risk minimisation activities	<Enter a date>	
	ANNEX 11 Mock up examples	<Enter a date>	
	ANNEX 12 Other supporting data	<Enter a date>	

** A new RMP version number should be assigned each time any Parts/modules are updated*

Some modules of the RMP may be omitted (for eligible types of products see GVP V table V.2) if the RMP relates only to products falling into these categories. In these circumstances leave the date field blank and write "Not applicable" or "NA" in the version field

QPPV name ……

QPPV signature ……

Contact person for this RMP ……

E-mail address or telephone

number of contact person ……

There can only ever by ONE agreed RMP for a product or products. Wherever possible there should only be one additional submitted RMP version under evaluation. To facilitate this, MAHs are reminded that where possible "routine" updates of a RMP should NOT be submitted when there is already a version of a RMP being evaluated as part of an on-going procedure. A cover letter should be submitted instead stating that there is no change to the RMP version xx dated yy submitted as part of procedure.

Where a procedure would normally require the submission of an updated RMP as part of the dossier, but there is already another version under evaluation because of another procedure, it is also possible to submit a letter as stated above.

In some circumstances there may be a need to submit a third RMP which is a different version from both the agreed RMP and a second RMP version currently undergoing evaluation e.g. if new safety concerns have been recently identified or if a new indication requires different risk minimisation measures. In this case different versions of a RMP will be simultaneously under evaluation. The purpose of this section is to provide oversight.

Overview of versions:

Version number of last agreed RMP:

Version number	<Enter a version no>
Agreed within	<Indicate procedure>

Current RMP versions under evaluation:

RMP Version number	**Submitted on**	**Submitted within**
<Insert number>	<Enter a date>	<indicate procedure number>
… etc.		

For each product in the RMP

Invented name(s) in the European Economic Area (EEA)	
Authorisation procedure	<indicate procedure>
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) in the EEA Current (if applicable)	
Proposed (if applicable)	
Posology and route of administration in the EEA Current (if applicable)	
Proposed (if applicable)	
Pharmaceutical form(s) and strengths Current (if applicable)	
Proposed (if applicable)	

Country and date of first authorisation worldwide	<Enter a country> <Enter a date>
Country and date of first launch worldwide	<Enter a country> <Enter a date>
Country and date of first authorisation in the EEA	<Enter a country> <Enter a date>

Is the product subject to additional monitoring in the EU? Yes ☐ No ☐

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

This should normally be completed for each indication. If a medicine has an indication for both prevention and treatment of the same disease (e.g. malaria) or for one disease but used in combination with different other therapies (oncology), it may be appropriate to include the "linked" indications together.

If the indication targets a subpopulation of those with the disease, provide the information for the target population as well as the disease as a whole e.g. patients with metastatic breast cancer who have failed one or more prior treatment.

If a disease can target both sexes, despite being predominately in one, information should be provided for both – e.g. breast cancer –unless it is a medicine contraindicated in one sex.

Indication

Brand names of concerned products (with this indication)

SI.1 Epidemiology of the disease

This may discuss inter-regional (e.g. EU, US, Asia, Africa etc.) variations but have a prime focus on the EU. If the epidemiology varies across countries within the EU, this should be discussed.

- Incidence and prevalence
- Demographics of the target population – age, sex, race/ethnic origin.
- Risk factors for the disease
- Main treatment options
- Mortality and morbidity (natural history)

SI.2 Concomitant medication(s) in the target population

Discuss other medications frequently used with the medicinal product either to treat the disease or complications of it (e.g. anti-hypertensives will frequently be used alongside hypoglycaemic medication in the treatment of diabetes; some oncology products are always used in combination etc.).

SI.3 Important co-morbidities found in the target population

Provide incidence, prevalence and mortality. If the incidence of a co-morbid disease commonly found in the target population is increased compared with the incidence in the general population of the same age/sex as a result of the disease itself, this should be specifically discussed (e.g. for a medicinal product to treat rheumatoid arthritis,

the incidence of coronary heart disease is increased in people with rheumatoid arthritis compared with that seen in patients without RA of the same age and sex)

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

This module should present a summary of the important non-clinical safety findings. Where studies have "negative" findings, these should be mentioned if of relevance to the target population (e.g. negative reproductive toxicity). 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: • Single and repeat-dose toxicity, • reproductive (must be discussed if medicine might be used in women of child-bearing potential) • developmental toxicity • nephrotoxicity • hepatotoxicity • genotoxicity • carcinogenicity	
General safety pharmacology: • cardiovascular (including potential for QT interval prolongation) • nervous system • etc.	
Mechanisms for drug interactions	
Other toxicity-related information or data	

Specify whether there is a need for additional non-clinical data if the medicinal product(s) is/are to be used in special populations

SII Conclusions on non-clinical data

List of safety concerns from non-clinical data that have:

- been confirmed by clinical data
- have not been adequately refuted by clinical data
- which are of unknown significance
- or where further research needed

Safety concerns
Important identified risks (confirmed by clinical data)
Important potential risks (not refuted by clinical data or which are of unknown significance)
Missing information

These safety concerns should be carried forward to Part II Module SVIII.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Provide details of how the authorised indications and target populations have developed during the lifecycle for the product(s) within this RMP. This should include:

- Original indication /product name(s)
- New populations e.g. extensions of indications/ new products
- Any other significant developments – e.g. route of administration

SIII.2 Clinical Trial 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:

- randomised, blinded trial population only
- all clinical trial populations (including open extension)

*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. When the reason for providing an updated RMP is a new population (either extension of indication or a new product with the same active substance) or a new strength or formulation, the new data should be presented separately first, as well as being included in the "total" tables.*

Data should be provided in an appropriate format – either in a table or graphically. The categories below are suggestions and tables/graphs should be tailored to the product. When patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/sex/ethnic original tables. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for the discrepancy.

If there is only one indication, tables 2, 4, 7, 9 and 11 do not need to be provided. Similarly table 6 need not be provided if only one product in the RMP.

Table 1: Duration of exposure (by indication)		
Indication 1 (person time should only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

Table 1: Duration of exposure (by indication)		
Indication 2 (person time should only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

Table 2: Duration of exposure (totals)		
Total exposed population (person time should only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

Table 3: By dose (by indication)		
Indication 1		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2 etc.		
Total		
Indication 2		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2 etc.		
Total		

Table 4: By dose (totals)		
Total Population		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 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 mature patients 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 5: By age group and gender (by indication)				
Indication 1				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				
Indication 2				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 6: By age group and gender (by product)				
Total population by medicinal product 1				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				
Total population by medicinal product 2				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 7: By age group and gender (totals)				
Total population				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 8: By ethnic or racial origin (by indication)		
Indication 1		
Ethnic/racial origin	Persons	Person time
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		
Indication 2		
Ethnic/racial origin	Persons	Person time
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 9: By ethnic or racial origin (totals)		
Total population		
Ethnic/racial origin	Persons	Person time
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 10: Special populations (by indication)		
Indication 1		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism (specify)		
Immuno-compromised		
Indication 2		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism (specify)		
Immuno-compromised		

Table 11: Special populations (totals)		
Total population		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism (specify)		
Immuno-compromised		

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

This module should discuss the limitations of the clinical trial population in relation to predicting the safety of the medicinal product(s) in the market place. The titles in SIV.3 below are suggestions and the discussion should be tailored to the medicinal product and its intended use and so may include other categories where there has been limited or no research. Limitations may also arise due to use in a different setting.

SIV.1 Limitations of adr detection common to clinical trial development programmes

Clinical trial development programmes are unlikely to detect the following types of adverse reactions due to well-known inherent limitations. Based on the number of patients exposed, the duration of patient exposure, total dose of medicine, action of medicine etc., discuss what could have been detected.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	<E.g. 12,600 patients were exposed over the whole CT programme>	<E.g. ADRS with a frequency greater than 1 in 4,200 could be detected if there were no background incidence>
Due to prolonged exposure	<E.g. 3000 women were exposed to X for more than 4 years during which time there were no cases of endometrial carcinoma. 42 women in the treated experienced endometrial hyperplasia compared with 35 in the non-exposed group (2000)>	<E.g. There does not appear to be an effect on endometrial proliferation during the first 4 years of treatment. X is thought to ……etc.>
Due to cumulative effects	<e.g. specific organ toxicity>	
Which have a long latency		

SIV.2 Effect of exclusion criteria in the clinical trial development plan

Discuss the main exclusion criteria across the clinical trial development programme. (This should not be a list of exclusion criteria by trial but a discussion on the effect of exclusion criteria across the clinical trial programme and the implications for treatment of the target population).

Exclusion criteria which will remain as contraindications	
Criteria	Implications for target population
1	
2 etc.	

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
1		
2 etc.		

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

These categories are suggested headings as they are typically under-represented in the clinical trial programme. Their relevance will depend upon the medicinal product, the indication and the development programme. There may be other relevant categories which are applicable.

Children

Special consideration should be given to the experience in different paediatric age groups – e.g. ICH-E11 - since these relate to different physiological and anatomical development stages. If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- Pre-term newborns
- Neonate (birth to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 years to e.g. 11 years)
- Adolescents (e.g. 12 years to 17 years)

Elderly

Implications on the use in patients of 65 and older should be discussed with appropriate consideration to the top ranges of the age spectrum. The effect of individual impairment should be discussed in the sections below but the effects of multiple (minor) co-existing impairments and also adverse reactions of particular concern in the elderly should be discussed.

- Use in different age ranges: e.g. 65-74, 75-84, >85
- Need for laboratory screening prior to use
- Effect of multiple co-existing impairments

- Adrs of special concern – e.g. dizziness, CNS effects
- Effect of multiple medications

Pregnant or breast feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast feeding should be discussed. If contraception was a clinical trial requirement the following should also be discussed:

- Number of pregnancies and outcomes
- Analysis of why contraceptive measures failed – i.e. consideration of whether human error or an interaction between product and e.g. oral contraceptives
- Implications for use under less controlled conditions (i.e. if measures failed under the relatively strict conditions of a trial, what will happen in real life, and if necessary suggestions for improvement)

Patients with hepatic impairment

Patients with renal impairment

Patients with other relevant co-morbidity e.g.

- Cardiovascular
- Immuno-compromised including transplant patients

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Sub-populations carrying known and relevant polymorphisms

The extent of pharmacogenetic effects and the implications of genetic biomarker use in the target population should be discussed where relevant. The implications for patients with/without a specific genetic marker/specific mutation or with unknown status should be stated - in particular where the indication requires genetic testing.

Patients of different racial and/or ethnic origin

*The implications for use in patients with different racial and/or ethnic origins should be discussed. In particular differences in the frequency or types of gene variants for drug metabolising enzymes may give rise to important differences in pharmacokinetics and/or frequency of adverse reactions. This variations in frequencies of particular alleles may have implications for drug use or for pre-treatment testing in patients of particular populations – e.g. HLA-B*1502 allele is associated with severe cutaneous adverse reactions to carbamazepine and is found in approximately 10% in some Asian populations but rarely in those of European descent.*

SIV.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information

Where the missing information from the clinical trial programme could constitute an important risk to the target population it should be considered to be a safety concern and should be stated here. If the missing information has been adequately investigated outside of the clinical programme this should be noted (with cross reference to the appropriate RMP section) in the comment section. Only safety concerns which are still outstanding should be carried through to RMP Part II Module SVIII.

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Safety concern	Comment	Yes/No
1		Choose one of the following: • Yes • No
2 etc.		Choose one of the following: • Yes • No

Part II: Module SV - Post-authorisation experience

The purpose of this RMP module is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP module SIV. It should also include brief information on the number of patients included in completed or on-going observational studies conducted either to elucidate a safety issue or for drug utilisation purposes. It is appreciated that detailed data may not be available. These tables provide guidance on how the data might be provided when available. Details of significant actions taken to update information on the safety of the medicinal product should also be provided in this module.

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

List any 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.

The list should be cumulative but newly taken action (since last update to the module) should be presented separately first, as well as being in the cumulative list. Roll-out in multiple countries of a new safety statement initiated by the MAH can be presented as one action (but list all countries and range of dates e.g. March-September 2011.) Comments may be added if the regulatory action is not applicable to certain products/formulations as authorised in the EU.

Table 1. Detailed description of action taken since last update to this module

Safety issue	
Background to issue	
Evidence source	
Action taken	
Countries affected	
Date(s) of action	

Table 2. Cumulative list

Safety concern 1			
Country(ies)	Action taken	Comment	Date(s)

Safety concern 2 etc.			
Country(ies)	Action taken	Comment	Date(s)

SV.2 Non-study post-authorisation exposure

Where possible, data on patients exposed post marketing should be provided based on market research. When the number of persons is calculated on the basis of sales data, details and justification should be provided of the measure used to calculate exposure. Tables should be provided for each indication and route of administration where possible.

SV.2.1 Method used to calculate exposure

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

SV.2.2 Exposure

By age group and gender				
Indication				
Age Group	Persons		Exposure (e.g. packs or person years)	
	M	F	M	F
Age group 1				
Age group 2				
Etc.				

By indication		
	Persons	Exposure (e.g. packs or person years)
Indication 1		
Indication 2		
Etc.		

By route of administration		
	Persons	Exposure (e.g. packs or person years)
Oral		
intravenous		
Etc.		

By dose		
Indication		
	Persons	Exposure (e.g. packs or person years)
Dose level 1		
Dose level 2		
Etc.		

By country		
Indication		
	Persons	Exposure (e.g. packs or person years)
EU		
Non-EU		

If possible, EU use should be broken down into country or sales area. Note the categories provided, are suggestions only and other relevant variables can be used e.g. oral versus i.e., duration of treatment etc.

SV.3 Post-authorisation use in populations not studied in clinical trials

Where there are data on post-authorisation use in the special populations identified in RMP module SIV as having no or limited exposure in clinical trials, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label. Comment on any differences in benefit or risk seen between the special population and the target population as a whole.

Paediatric use		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• Pre-term new-borns • Neonates (birth to 27 days) • Infants and toddlers (1 month to 23 months) • Children (2 years to e.g. 11 years) • Adolescents (e.g. 12 years to 18 years)		
Data source		
Method of calculation		

Elderly use		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• 65 – 74 years • 75 – 84 years • 85+ years		
Data source		
Method of calculation		

Pregnant or breast feeding women		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• Pregnant • Breast feeding		
Data source		
Method of calculation		

Hepatic impairment		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• Mild • Moderate • Severe		
Data source		
Method of calculation		

Renal impairment		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• Mild • Moderate • Severe		
Data source		
Method of calculation		

Other use (specify)		
Estimated use	Number	Comment on any variation in benefit or risk from overall target population
• Specify category • Specify category • Specify category		
Data source		
Method of calculation		

SV.4 Post-authorisation off-label use

Post marketing, updates to the safety specification, should include information on EU off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the authorised product information for a medicinal product. Off-label use includes use in non-authorised paediatric age categories.

EU off-label use			
Off label category	Country	Source of information	Comment
<E.g. Use in dysmenorrhoea (non-authorised indication)>	<E.g. Italy>	<E.g. Poseidon: Drug utilisation study using Emilia Romagna NHS drug prescription in general practice, Italy>	<E.g. Epidemiological study in electronic health care records found 15 women (1.7%) prescribed painoprofen for dysmenorrhoea out of total of 975 users>

SV.5 Epidemiological study exposure

Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included.

Study title and study type (e.g. cohort or case/control)	**Objectives**	**Population studied (data source and country)**	**Duration (study period)**	**Number of persons (in each group or of cases and controls) and person time (if appropriate)**	**Comment**
<E.g. Poseidon (cross sectional DUS)>	<E.g. Investigate utilisation of painoprofen in General Practice in Italy>	<E.g. Emilia Romagna NHS drug prescription in general practice, Italy>	<E.g. 3 month time window>	<E.g. 975 users from study population of 3.5M>	<E.g. Study report in annex 5>
Study 2 etc.					

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

SVI.1 Potential for harm from overdose

Discuss the potential for harm from overdose – either intentional or accidental. Give special attention to medicinal products where there is increased risk of harm – either where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population. Where harm from overdose has occurred during clinical trials, this should be explicitly mentioned. Where appropriate, overdose should be included as a safety concern in RMP Module SVIII

SVI.2 Potential for transmission of infectious agents

The applicant/marketing authorisation holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for the transmission of live virus should be discussed. For advanced therapy medicinal products, a cross reference to RMP modules SVII (ATMP) may be made.

SVI.3 Potential for misuse for illegal purposes

Discuss the potential for use as a recreational drug or facilitating assault etc. If appropriate discuss the means of limiting this in the risk minimisation plan.

SVI.4 Potential for medication errors

If necessary, this section may be completed separately for each product.

SVI.4.1 Description of medication errors during the clinical trial programme

Product name(s)				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment

SVI.4.2 Preventive measures for the final product(s) being marketed

Discuss how the following errors have been prevented in the design of the product, packaging, labelling etc.

- Prevention of error due to wrong medication
- Prevention of error due to wrong dose (strength, form, concentration)

- Prevention of error due to wrong route of administration

SVI.4.3 Effect of device failure

For products where a device is an integral part of the administration of the product.

SVI.4.4 Reports of medication errors with the marketed product(s)

Product name(s)				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment

Where multiple strengths, posologies or concentrations are available, or where different products have different formulations, reconstitution differences etc., consideration should be given to including "medication error" as a safety concern.

SVI.5 Potential for off-label use

The potential for off-label use should be discussed. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

SVI.6 Specific Paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

Any issues identified in paediatric investigation plans should be detailed and the relevance to the indications covered by this RMP discussed. Include details of how paediatric investigation plan recommendations have been considered. Cross reference may be made to other RMP Modules.

Product Name and PIP <Number>		
Issue (safety or long term efficacy)	Background	Relevance to indications covered in this RMP and how, if appropriate, it will be addressed.

SVI.6.2 Potential for paediatric off-label use

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all

paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed. If there are limited treatment options it should not be assumed that clinicians will adhere to the labelled indication so it is important that potential paediatric issues are discussed and consideration given for their inclusion as a safety concern. Any actual use should be discussed and cross reference to other relevant RMP sections provided.

SVI.7 Conclusions

Safety concerns from this module (to be carried through to Part II Module SVIII)	
Safety concern	Comment

Part II: Module SVII - Identified and potential risks

Non-ATMP version

This RMP module should provide more information on the important identified and potential risks. This RMP section should be concise and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the summary of product characteristics (SmPC). It should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and which is/is likely to be included in the contraindications, or warnings and precautions section of the summary of product characteristics (SmPC) should be included here. In addition, risks, which whilst not normally serious enough to require specific warnings or precautions, but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated, should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

For some products, disposal of the used product may constitute a safety concern, e.g. transdermal patches where there may be significant amounts of active substance remaining in the patch when it is discarded. There may also be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment, e.g. substances which are particularly hazardous to aquatic life which should not be disposed of in landfill sites.

Because of the need for different additional categories of risks to be considered with advanced therapy medicinal products, a different version of the template for RMP module SVII is available for products classified as advanced medicinal products. Only one version of the template of RMP module SVII should be used in a RMP.

SVII.1 Newly identified safety concerns (since this module was last submitted)

Safety concern
Details
Source
New studies proposed in pharmacovigilance plan? Yes/No
New risk minimisation actions proposed? Yes/No

SVII.2 Recent study reports with implications for safety concerns

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections and modules of the safety specification as appropriate with detailed information on the risk provided in SVII.3.

Details of the above safety concerns should also be provided below.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

This RMP section should provide information on the important identified and important potential risks. This section should be concise and should NOT be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual content of section 4.8 of the summary of product characteristics. For most RMPs involving single products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns, e.g. accidental IV administration could be a safety concern in a single product with both oral and subcutaneous forms. It may be appropriate to include risks associated with a significant change to a manufacturing process (particularly for biologicals) and risks associated with medication error

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

- Risks relating to the active substance

This would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of products.

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

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

- Risks relating to a specific target population

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and

sexual development which would not be relevant to a product intended solely for adult patients.

- Risks associated with switch to non-prescription status

For each important identified and important potential risk[2] provide the following information if available:

NB: If preferred this can be provided outside of the table format using the sections (as detailed in the first column) as paragraph headings.

Identified / potential Risk[2] <>	
Frequency with 95 % CI	*State clearly which frequency parameter is being used e.g. incidence rate or incidence risk and the data source e.g. blinded clinical trial population, epidemiological study. For identified risks incidence should be presented for the whole population and relevant subpopulation categories.* *(see also section V.B.8.7.3 of GVP Module V)* *Where there are clear differences in rates between populations, this should be discussed*
Seriousness/outcomes	*Tabulate the distribution of outcomes e.g. % fatal, % recovered/with/without treatment/sequelae, % not recovered, % hospitalised etc.*
Severity and nature of risk	*e.g. tabulate grades of severity where available*
Background incidence/prevalence	*Background incidence/prevalence of the risk in the unexposed target population(s)*
Risk groups or risk factors	*Describe patient factors, dose, time or other factors where available including additive or synergistic factors*
Potential mechanisms	*Describe*
Preventability	*Provide data on predictability or preventability of ADR, effect of known risk factors, mitigation through early detection*
Impact on individual patient	*effect on quality of life*
Potential public health impact of safety concern	*Describe or enumerate if possible, using e.g. Numbers Needed to Harm and/or expected number of patients affected, hospitalisations, fatalities given the*

[2] For definitions see Good Vigilance Practices (GVP) Module V, chapter V.B.1.

Identified / potential Risk[2] < >	
	predicted population use.
Evidence source	*Identify, briefly describe and cross refer to supporting data in CTD or annex*
MedDRA terms	*Terms used in Annex 1 for post marketing surveillance*

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Discuss the main routes of metabolism and elimination and the potential for interactions due to effects on CYP enzymes, drug transporters etc.

SVII.4.2 Important identified and potential interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. Important interactions with herbal medicines or with food should also be discussed.

Interacting substance(s)	**< >**
Effect of interaction	
Evidence source	
Possible mechanisms	
Potential health risk	
Discussion	

Consider including "interactions" as a safety concern in Part II Module SVIII.

SVII.5 Pharmacological class effects

Identify risks which are believed to be common to the pharmacological class.

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

For risks which have been included above in "Details of important and identified and potential risks from clinical development and post-authorisation experience" above, provide the following details below.

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (source of data / journal reference)	Comment
Risk 1		<E.g. Product A Product B Product C Review of adverse reactions BMJ 2008: 5; 214-217>	
Risk 2 etc.			

SVII.5.2 Important pharmacological class effects not discussed above

The table below should be provided for each important risk which has not been included in RMP module SVII "Details of important identified and potential risks from clinical development and post-authorisation experience" (above) but which is believed to be common to the pharmacological class. If an important potential risk, associated with other members of the pharmacological class, is not thought to be a safety concern with the medicinal product this should be justified and supporting evidence provided.

Potential Risk < >	
Seriousness/outcomes	
Severity and nature of risk	*e.g. tabulate grades of severity where available*
Frequency with other members of the same or similar pharmacological class with 95 % CI	
Risk groups or risk factors	*Describe use, dose, time and susceptibility data or other factors where available.*
Potential mechanisms	*Describe*
Comment	

Part II: Module SVIII - Summary of the safety concerns

A summary should be provided of the safety concerns identified in previous Modules (SII, SIV, SVI, and SVII) of Part II. A safety concern may be an:

- important identified risk;
- important potential risk; or
- missing information.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, similar to the presentation of risks in RMP module SVII, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- safety concerns relating to the active substance;
- safety concerns related to a specific formulation or route of administration;
- safety concerns relating to the target population;
- risks associated with switch to non-prescription status.

Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

Table 3. 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/ studies which are intended to identify and/or characterise safety concerns. 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.

Some safety concerns may be well characterised in which case routine PhV will be sufficient. Depending upon the safety concern, and areas to be investigated, a PhV Plan will often include epidemiological (non-interventional) studies (such as cohort, case control, registries, 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.

In the PhV Plan, section III.1 reviews each safety concern and what areas need investigation whereas III.4 gives details of the individual studies and milestones. Section III.2 provides details of any activities aimed at measuring the effectiveness of risk minimisation activities. The results of any studies in the PhV Plan should be briefly summarised in section III.3. If the study results concern the effectiveness of risk minimisation, brief results should be provided in section III.3. If the results suggest that the risk minimisation measure is failing in its objectives, this should be discussed with the root cause analysis and proposal for rectification in Part V of the RMP. Section III.5 summarises the entire PhV plan – both completed, on-going and planned activities.

III.1 Safety concerns and overview of planned pharmacovigilance actions

For each safety concern in Part II SVIII, provide details of specific areas that still need confirmation or further investigation – e.g. confirmation of incidence, investigation of risk factors. It may be that for a well characterised safety concern that there are no areas which need investigating in which case "none" should be written in column 1 and the only proposed action will be "routine pharmacovigilance". Some areas may need more than one activity to characterise a safety concern with different activities having different objectives. If a specific questionnaire is planned for collecting structured data on a safety concern of special interest this is still considered to be routine but should be mentioned and a mock up provided in RMP annex 7. A requirement to report on a specific adverse drug reaction at defined intervals resulting from a previous evaluation (e.g. PSUR/PBER) will be considered as routine pharmacovigilance but should be detailed in the table against the specific safety concern. Outstanding additional pharmacovigilance activities should be detailed in section III.4.

Safety concern 1		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
1		
2		
3 etc.		

Safety concern 2 etc.		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
1		
2		
3 etc.		

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Where there are risk minimisation measures which require the use of non-routine pharmacovigilance activities to measure the effectiveness, details should be provided here.

Risk minimisation measure		
Component measured	Activity(ies)	Rationale
Component 1		
Component 2 etc.		

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

This is a summary of completed studies and/or activities since the last update of the Pharmacovigilance Plan. The concise study report should be provided in RMP annex 9.

Study / activity title	
Safety concern(s)/risk minimisation measure investigated	
Brief summary of results	
Implications	

III.4 Details of outstanding additional pharmacovigilance activities

The MAH should propose categories for new additional PhV studies/activities in the pharmacovigilance plan. These categories will be confirmed or recategorised during the evaluation of the RMP. Updates of the RMP should reflect the categorisation as agreed by CHMP/national competent authority (along with any proposed new studies).

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Table 4. Imposed activities considered key to the benefit risk of the product

	Description of activity (or study title if known)	**Milestone(s)**	**Due Date(s)**
1		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>
2 etc.		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>

III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

Table 5. Specific obligations

	Description of activity (or study title if known)	**Milestone(s)**	**Due Date(s)**
1		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>
2 etc.		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>

Non-interventional studies included in categories 1 and 2 are subject to the supervision exercised under Articles 107 (m)-(q) of Directive 2001/83.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

These are category 3 activities that are conducted or financed by the MAH to address particular safety concerns but do not include studies which are imposed or which are specific obligations (i.e. categories 1 or 2 above). These activities may include trials or studies which may be on-going (e.g. from clinical trials where the activity would be to provide a report) or be planned where the activity is to conduct the study. This would include studies or activities requested by another Regulatory authority where the results are expected to provide

information relevant to existing areas of uncertainty. Studies which have been specifically requested by the CHMP/PRAC (which are not conditions of the marketing authorisation) or which may be suggested by the MAH to investigate a safety concern should also be included here. Studies to measure the effectiveness of risk minimisation measures would normally fall into this category.

Table 6. Required additional pharmacovigilance activities

	Description of activity (or study title if known)	**Milestone(s)**	**Due Date(s)**
1		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>
2 etc.		1.(e.g. protocol submission)	<Enter a date>
		2.(e.g. study start)	<Enter a date>
		3.(e.g. study finish)	<Enter a date>
		4. (e.g. final report)	<Enter a date>

III.4.4 Stated additional pharmacovigilance activities

These are activities which may provide additional supporting evidence but are not primarily intended to investigate a specific safety concern. This would include drug utilisation studies being conducted as a condition for reimbursement, studies requested by other regulatory authorities for reasons not related to a specific safety concern or safety studies carried out by a third party which the MAH is aware of, but is not providing funding (unconditional or otherwise) or other support.

Table 7. Stated additional pharmacovigilance activities

	Description of activity (or study title if known)	**Expected date of report**
1		<Enter a date>
2		<Enter a date>
3 etc.		<Enter a date>

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

This should be a complete overview of all on-going and planned studies in categories 1-3.

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
<E.g. CRUCIAL Cancer Registry at University College IdAho Liver unit (non-interventional cohort, 3)>	<E.g. To investigate long term survival, time to progression, safety profile and QoL in patients with primary liver cancer or solid tumour metastases>	<E.g. Bradycardia, thrombosis, leukopenia, use in patients with renal impairment, long term safety>	<E.g. Protocol submitted to PRAC>	<E.g. Interim reports planned June 2013, 2017 Final study report Dec 2020>
<E.g. Validation of antibody test (non-clinical, 3)>	<E.g. Comparison of Supertest kit with current gold standard>	<E.g. Development of antibodies>	<E.g. Planned start March 2013>	<E.g. Final study report December 2013>

III.5.2 Table of completed studies / activities from the Pharmacovigilance Plan

This should be a complete overview of all completed studies in categories 1-3.

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date of submission of final study report
<E.g.ABC-124 (randomised controlled trial, 3)>	<E.g. Compare time to disease progression with 3 different doses of Compare safety profile of different doses>	<E.g. Bradycardia, development of antibodies, Use in patients with renal impairment.>	<E.g. Completed. Final study report submitted>	<E.g. Final study report submitted 31st March 2009>

Part IV: Plans for post-authorisation efficacy studies

IV.1 Applicability of efficacy to all patients in the target population

Based on the data in RMP Part II modules SIII, SIV and SV, the MAH/Applicant should very briefly discuss whether there are any gaps in knowledge about efficacy in the target population and whether there is a need for further efficacy studies post-authorisation. This should NOT include efficacy studies aimed at extending the indication.

Factors which might be relevant include:

- Applicability of the efficacy data to all patients in the target population – e.g. if 98% of patients in trials were Caucasians discuss whether efficacy is likely to be same in other races in target population
- Factors which might affect the efficacy of the product in everyday medical practice – e.g. use in general practice rather than the clinical trial hospital out-patient setting
- Long term efficacy
- Any evidence that there might be variability in benefits of treatment for sub populations.

IV.2 Tables of post-authorisation efficacy studies

The MAH/Applicant should list any post authorisation efficacy studies which are proposed by the MAH/Applicant in relation to the above and also include those studies which have been imposed by the CHMP/NCA or which are Specific Obligations. A synopsis of the protocols should be provided in Annex 8.

Table 8. Efficacy studies which are specific obligations and/or conditions of the MA

Description of study (including objectives and study number)	**Milestone(s)**	**Due Date(s)**
	1.(e.g. protocol submission)	<Enter a date>
	2.(e.g. study start)	<Enter a date>
	3.(e.g. study finish)	<Enter a date>
	4. (e.g. final report)	<Enter a date>

Table 9. Other efficacy/effectiveness studies

Description of study (including objectives and study number)	**Milestone(s)**	**Due Date(s)**
	1.(e.g. protocol submission)	<Enter a date>
	2.(e.g. study start)	<Enter a date>
	3.(e.g. study finish)	<Enter a date>
	4. (e.g. final report)	<Enter a date>

IV.3 Summary of Post authorisation efficacy development plan

This should be a complete overview of all studies (on-going, planned)

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports

IV.4 Summary of completed Post authorisation efficacy studies

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (Completed, Study report submitted)	Date of submission of final study report

Part V: Risk minimisation measures

Each safety concern identified in module SVIII "summary of the safety specification" should be addressed. If no risk minimisation measures are proposed, then "none proposed" should be entered against the objective.

If several components make up one risk minimisation measure (e.g. a pregnancy prevention plan may have educational material for health care professionals and patients, algorithms for deciding on child-bearing potential, patient reminder cards etc.) these should be grouped together.

For each safety concern, provide details of what criteria will be used to judge whether risk minimisation measures are a success e.g. fewer than 2 pregnancy reports in period y, no cases of liver failure reported, drug utilisation study showing <5% off-label use etc.

Further guidance on risk minimisation measures can be found in GVP Module XVI and CIOMS IX.

V.1 Risk minimisation measures by safety concern

Safety concern	
Objective(s) of the risk minimisation measures	
Routine risk minimisation measures	(Proposed) text in SmPC <E.g. Dose reduction for ……. in section 4.2 of the SPC…….. Warning in sec tion 4.4 to…… Listed in section 4.8>
	Comment (e.g. on any differences between SmPCs)
	Other routine risk minimisation measures <E.g. Prescription only medicine Use restricted to physicians experienced in the treatment of…….>
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	*If a study is planned, this should also be included in Part III.2 Additional PhV activities to assess effectiveness of risk minimisation measures*
Criteria for judging the success of the proposed risk minimisation measures	
Planned dates for assessment	
Results of effectiveness measurement	Provide latest assessment at each update of the RMP. For risk minimisation measures where formal studies are planned, any results should be mentioned in Part III.2 with the implications discussed here and any remedial actions in V.2
Impact of risk minimisation	
Comment	

V.2 Risk minimisation measure failure (if applicable)

List the safety concerns and risk minimisation measures which are judged to have failed.

Safety concern	Risk minimisation measure

V.2.1 Analysis of risk minimisation measure(s) failure

When risk minimisation measures for a safety concern are thought to be inadequate, a root cause analysis of where it is failing should be undertaken

Safety concern	
Risk minimisation measure(s)	
Component 1	Analysis
Component 2 etc.	Analysis
Discussion	

V.2.2 Revised proposal for risk minimisation

Based on the analysis of why the risk minimisation activities were inadequate, a proposal should be made for new (or revised) risk minimisation measures for the safety concern

Safety concern	
Objective(s) of the risk minimisation activities	
Routine risk minimisation activities	Synopsis of (proposed) text in SmPC
	Comment (e.g. on any differences between SmPCs)
	Other routine risk minimisation activities
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale
Comment on how revised proposals will address failings	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	*If a study is planned, this should also be included in Part III: Additional PhV activities to assess effectiveness of risk minimisation measures*
Criteria for judging the success of the proposed risk minimisation measures	

V.3 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	From V.1 “proposed text in SmPC” and “other routine risk minimisation measures”	From V.1 (list)
	<E.g. Dose reduction for ……. in section 4.2 of the SPC…… Warning in section 4.4 to…… Listed in section 4.8 Prescription only medicine Use restricted to physicians experienced in the treatment of……>	

Part VI: Summary of the risk management plan by product

A separate RMP Part VI should be provided for each product in the RMP.

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Copy table from Part I: SVIII

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

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Copy table from III.5.1.

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
<E.g. CRUCIAL Cancer Registry at University College IdAho Liver unit (non-interventional cohort, 3)>	<E.g. To investigate long term survival, time to progression, safety profile and QoL in patients with primary liver cancer or solid tumour metastases>	<E.g. Bradycardia, thrombosis, leukopenia, use in patients with renal impairment, long term safety>	<E.g. Protocol submitted to PRAC>	<E.g. Interim reports planned June 2013, 2017 Final study report Dec 2020>
<E.g. Validation of antibody test (non-clinical, 3)>	<E.g. Comparison of Supertest kit with current gold standard>	<E.g. Development of antibodies>	<E.g. Planned start March 2013>	<E.g. Final study report December 2013>

VI.1.3 Summary of Post authorisation efficacy development plan

Copy table IV.3 from Part IV

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status	Date for submission of interim or final reports

VI.1.4 Summary table of Risk Minimisation Measures

Copy table from Part V: V.3

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

(Maximum 150 words per indication)

Abbreviated lay language version of RMP Part II Module I.

VI.2.2 Summary of treatment benefits

The summary of treatment benefits should be in lay language and non-promotional. The text should not exceed a maximum of 200 words (up to 300 if multiple indications). The following should be considered for inclusion:

- *Describe briefly each pivotal study, including total participant numbers (randomised figure where applicable). Explain the primary endpoint in lay language.*
- *If there are multiple indications, use bullet points to separate the studies per indication. If there are several studies for one indication with a similar design, in some cases these may be described together and the total patient numbers combined to stay concise.*
- *For each study, describe the primary endpoint results directly after the description of the study (either in the same paragraph, or a separate paragraph if needed). When using percentages, give patient numbers in brackets.*

<E.g. The average survival time for patients in the main study treated with 475 mg of drug x in addition to drugs y and z increased by 19.5 months to 55.5 months compared with treatment 2 (36 months) and 17 months (57.5 months) compared with treatment 3 (40.5) months.>

VI.2.3 Unknowns relating to treatment benefits

(1 short paragraph per indication of 50 words maximum)

A short summary of the applicability of efficacy to all patients in the target population can be provided in lay language. This should be a précised version of Part IV IV.1 written for the lay reader. It should describe very briefly any relevant parts of the target population where experience is limited and whether efficacy is expected to be different in these people – e.g. factors such as age, sex, race, and organ impairment. If there is evidence that efficacy is either enhanced or reduced (e.g. ACE inhibitors and the Afro-Caribbean population) this should be stated.

<E.g. In the main and supporting studies nearly all patients were white Caucasians aged between 52 and 86 with most patients aged over 65. There is no evidence to suggest that results would be any different in non-white patients or in younger patients unable to tolerate high dose chemotherapy.>

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
<Safety concern in lay language (medical term)>	<Brief summary in lay language>	<Whether risk can be minimised or mitigated, and how>
<E.g. Damage to the nerves in hands and feet (peripheral neuropathy)>	<E.g. Approximately one in two people treated with x will experience some form of nerve damage which may increase to three out of four people after 12 months of treatment. The nerve damage varies from mild tingling and altered sensation to irreversible disabling damage in the most severe cases. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy. >	<E.g. Yes, by monitoring for early symptoms >
<E.g. Blood clots (thromboembolic events {TEE})>	<E.g. These may affect the arteries or veins. In the veins this may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries. Patients with cancer who are	<E.g. Yes with preventative anti-thrombotic medicines >

Risk	What is known	Preventability
	being treated with oestrogen are already at higher risk of blood clots so it is difficult to assess what extra risk is caused by x.>	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
<E.g. Secondary primary cancers>	<E.g. Patients treated with X may be at an increased risk of developing new cancers. There are theoretical mechanisms and more patients treated with X developed new cancers than those not treated with X, but this could also be due to the fact that they live longer.>

Missing information

Risk	What is known
<E.g. Limited information on use in patients with kidney impairment>	<E.g. X itself is not eliminated to any significant extent by the kidney so it is unlikely that kidney impairment will lead to problems. Some of its metabolites are eliminated by the kidney so it is recommended that patients with severe renal impairment are monitored carefully. >

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for X can be found in the X's EPAR page

<This medicine has no additional risk minimisation measures>

<This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in X's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Risk minimisation measure(s)
Objective and rationale
• Summary description of main additional risk minimisation measures – key points
<E.g. Damage to the nerves in hands and feet (peripheral neuropathy) Healthcare Professional and patient education Objective and rationale Patients and HCPs to understand the risk of peripheral neuropathy and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: Use of electromyogram prior to and during treatment Importance of adherence to dosing recommendations Management of neuropathy including dose reduction and treatment discontinuation Direct HCP communication prior to launch ('Dear HCP' letter). Patient booklet will inform patients what the symptoms of nerve damage are and the importance of informing their HCP if any occur>

VI.2.6 Planned post authorisation development plan

From combined summary tables in Part III and Part IV

List of studies in post authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**

Studies which are a condition of the marketing authorisation

<None of the above studies are conditions of the marketing authorisation>

< <study(ies)> <is><are> <a> condition<s> of the marketing authorisation

Mention all studies in the table (including specific obligations) which are conditions of the MA.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
	At time of authorisation dd/mm/yyyy	Identified Risks Potential Risks Missing information	
<E.g. 7.0>	<E.g. 17/08/2012>	<E.g.Allergic conditions added as an identified risk Hypersensitivity removed as an identified risk Severe infection added as an identified risk Convulsions added as a potential risk>	<E.g. The previous term hypersensitivity was updated to allergic conditions to include angioedema and urticarial>

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Available in electronic format only

Annex 2 - SmPC & Package Leaflet

Current (or proposed if product is not authorised) EU (centralised/mutual recognition/decentralised/national) summary of product characteristics (SmPC) and package leaflet(s) for each product in the RMP.

If multiple versions are included for a product, they should show in which Member State(s) they are applicable. In addition, if available, a core SmPC should be provided with an overview of the changes applicable to the SmPC in each Member State

Annex 3 - Worldwide marketing authorisation by country (including EEA)

For each product in the RMP provide:

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action [1]	Date first marketed in country	Brand name(s)	Comments
	Choose one of the following: • Approved • Refused • Under review • Suspended • Expired • Withdrawn	<Enter a date>	<Enter a date>		If product has different routes of authorisation e.g. national + MRP in the EEA, note here which one applies

[1] Enter the date of the most recent change to the licence status: eg date of approval or date of suspension

A3.2 Licensing status in the rest of the world

Country	Current licence status	Date of licence action 1	Date first marketed in country	Brand name(s)	Comments
	Choose one of the following: • Approved • Refused • Under review • Suspended • Expired • Withdrawn	<Enter a date>	<Enter a date>		

Annex 4 - Synopsis of on-going and completed clinical trial programme

Study	**Description (Phase, short description of study (1 – 2 sentences including comparator name(s)/placebo))**	**Countries**	**Study design**	**Planned/actual number of patients**	**Duration of follow up**	**Estimated/ Actual completion date**
Main or pivotal studies						
<E.g. Study ABC>	<E.g. Study versus ibuprofen in adults with mild postoperative pain Phase III>	<E.g. Germany, USA, Chile>	<E.g. Randomised double-blind>	<E.g. 4075>	<E.g. 14 days>	<E.g. Jan 2005>
Further safety/efficacy studies						
Studies in special populations (e.g. paediatric, elderly)						

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population & study size	Duration of follow up	Milestones & dates	Status
						Choose one of the following: • Planned • Protocol under development • Protocol agreed • Data collection started • Data collection ended • Study completed

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Overview of included protocols

Study title	**Protocol status** [1]	**Version of protocol**	**Date of protocol version**
	Choose one of the following: • Draft • Approved • Final		<Enter a date>

[1]Draft = not approved or final

Approved = when agreed by PRAC or CHMP as appropriate

Final = final version when PRAC/CHMP agreement not required

Annex 7 - Specific adverse event follow-up forms

Provide forms

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Study title	**Protocol status** [1]	**Version of protocol**	**Date of protocol version**
	Choose one of the following: • Draft • Approved • Final		<Enter a date>

[1]Draft = not approved or final

Approved = when agreed by CHMP

Final = final version when CHMP agreement not required

Annex 9 - Newly available study reports for RMP parts III & IV

Include the study abstract. For non-interventional studies use the abstract format detailed in Module: VIII Post Authorisation Safety Studies of Good Pharmacovigilance Safety Studies

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

Mock up examples in English (or the National language if the product is only authorised in a single Member State) of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisations including those using the mutual recognition or decentralised procedure as applicable.

Annex 12 - Other supporting data (including referenced material)

Index of included material