European Medicines Agency
*Post-authorisation Evaluation of Medicines for Human Use*

London, 27/09/2006
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# Annex C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU – RMP)

This template provides advice on how the data requested in the Guideline, if ava able, hould be presented. It is anticipated that, particularly in section 1, all the informati will no be vailable or all drugs and that the type of product and where it is in its lifecycle will affec how mu h information can be provided.

| **Overview of EU Risk Management Plan Template** | |
|---|---|
| **Section** | |
| | Product information |
| 1 | Safety Specification |
| 2 | Pharmacovigilanc Plan |
| 3 | Evaluation of the n ed f risk m nimisation activities |
| 4 | Risk Minim ation Plan |
| 5 | Summar o the EU-RMP |
| 6 | Contact per n details |
| | |
| Annex 1 | Interfa between EU-RMP and Eudravigilance<br>*To b provided in electronic form only* |
| Annex 2 | C rrent (or roposed if initial EU-RMP) SPC, Package eaflet |
| Annex 3 | Syn psis of ongoing and completed clinical trial programme |
| Ann 4 | Synopsis of ongoing and completed pharmacoepidemiological study programme |
| nnex 5 | Protocols for proposed and ongoing studies in pharmacovigilance plan |
| Anne 6 | Newly available study reports |
| Anne 7 | Other supporting data |
| Ann x 8 | Details of proposed educational programme (if applicable) |

To be lid an EU-RMP MUST contain sections 1,2 & 3. With the exception of section 4 (which must e completed if additional risk minimisation activities are proposed) all sections should be p ovided. Annex 1 should be provided in electronic form only.

Please ensure that the data provided in this document are coded in MedDRA terms where appropriate and are consistent with those submitted electronically in the template attached in Annex 1.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 20
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

## PRODUCT DETAILS

| | |
|---|---|
| Invented name of the medicinal product (product short name): | |
| Active substance(s) (INN or common name): | |
| Pharmaco-therapeutic group (ATC Code): | |
| Medicinal Product Code (From EudraVigilance) | |
| Authorisation procedure(s) (central, mutual recognition, decentralised, national) | |
| Name of Marketing Authorisation Holder or Applicant: | |
| Date and country of first authorisation worldwide | |
| Date and country of first launch worldwide | |
| Date and country of first authorisation in the EEA | If diffe nt from above |
| Date and country of first launch in the EEA | If ferent from above |

ata loc point for EU – RMP | dd/mm/yyyy | Version |

| | |
|---|---|
| **Brief description of product (chemical class, mode of action etc)** | |
| **Indication(s)** | Current if applicable<br><br>Proposed if applicable |
| **Dosage** | Current or proposed for eac indic ion and duration of therapy |
| **Pharmaceutical form(s) and strength(s)** | |

# PART I

# 1. SAFETY SPECIFICATION

## Non-clinical

***1.1.1.*** *<Outline of safety concerns that have not been adequately addressed by clinica data or which are of unknown significance>; for example*

Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity neph otoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.)

General safety pharmacology (cardiovascular [including QT interval prol ngati ] nervous system, etc.)

Mechanisms for drug interactions

Other toxicity-related information or data

| SAFETY CONCERN (from non clinical studies) | RELEVANCE TO HUMAN U AGE |
|---|---|
| **<repeat dose toxicity>** | |
| **<reproductive toxicity>** *a summary of important findings(including negatives) should always be incl d if the drug is intended for use in women of childbearing age.* | |
| **<developmental toxicity>** | |
| **etc** | |

***1.1.2.*** *<Specify need f r add onal on-clinical data if the product is to be used in special population >*

## Clinical

# 1.2 Limitations of the human safety database

### *1.2.1.* *Exposure*

*Clinical trial exposure*

The following tables should be provided, separately for each indication with a summary table sh wing total exposure. Provide each table, where available, based on exposed (to medicinal produ t of interest) persons in:

a) randomised, blinded trial population only

b) all clinical trial populations (including open extension).

| **Table 1: BY DURATION** | | |
|---|---|---|
| INDICATION (or TOTAL) | | |
| Duration of exposure | Persons | Person t e |
| Cumulative Up to 1 m | | |
| Cumulative Up to 3 m | | |
| Cumulative Up to 6 m | | |
| Cumulative Up to 12 m | | |

| **Table 2: BY DOSE** | | |
|---|---|---|
| INDICATION (or TOTAL) | | |
| Dose of exposure | Persons | Person time |
| Dose level 1 | | |
| Dose level 2 | | |
| etc | | |

| **Table 3: BY AGE GR UP AND GENDER** | | | | |
|---|---|---|---|---|
| INDICATIO (or T AL) | | | | |
| Age group | Persons | | Person time | |
| | M | F | M | F |
| Age group | | | | |
| Age group 2 | | | | |
| e | | | | |

| **Table 4: Y ETHNIC ORIGIN** | | |
|---|---|---|
| INDICA ION (or TOTAL) | | |
| | Persons | Person time |
| Ethnic origin 1 | | |
| Ethnic origin 2 | | |
| etc | | |

| **Table 5: SPECIAL POPULATIONS** | | |
|---|---|---|
| INDICATION (or TOTAL) | | |
| | 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) | | |

Note the categories provided, are suggestions only and the tables should be tailored to the product, clearly identified and justified. For example, for parenteral administration, consider number of administrations e.g. 1, 2, 3 or more repeated exposures. For age and gender make explicit reference to paediatric and elderly populations.

*Epidemiological study exposure*

| **Study** | **Study type (eg cohort or case/control** | **Population studied** | **Duration (study period)** | **Number of persons (in each group or of cases and controls)** | **Person time (if appropriate)** |
|---|---|---|---|---|---|
| Study1 | | | | | |
| Study 2 | | | | | |
| etc | | | | | |

*Post marketing (non study) exposure*

Data on patients exposed post marketing should be provided based on market research where possible. When the number of persons is calculated on the basis of sale dat , details and justification should be provided of the measure used to calculate exposure T bles s uld be rovided for each indication where possible.

| **Table 1: BY AGE GROUP AND GENDER** | | | | |
|---|---|---|---|---|
| Indication | | | | |
| Age group | Persons | | Exposure (eg packs or person years) | |
| | M | | M | F |
| Age group 1 | | | | |
| Age group 2 | | | | |
| etc | | | | |

| **Table 2: BY DOSE** | | |
|---|---|---|
| Indication | | |
| | P sons | Exposure (eg packs or person years) |
| Dose level 1 | | |
| Dose level 2 | | |
| etc | | |

| **Table 3: BY C UNTRY** | | |
|---|---|---|
| Indication | | |
| | Persons | Exposure (eg packs or person years) |
| | | |
| 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 eg oral versus iv, duration of treatment etc.

## 1.3 Populations not studied in the pre-authorisation phase

For each pivotal and supporting study, list exclusion criteria for studies.

| Study number | No of patients exposed to this product in the study | Age range | Exclusion criteria for study |
|---|---|---|---|
| | | | |
| | | | |

The limitations of the human safety database should be discussed in terms of the relevan of inclusion and exclusion criteria and the populations actually studied in relation e tar t population(s). Where exclusion criteria are not proposed as contraindications to treatment thi should be discussed and justified. Populations to be considered for discussion should in lude but is not limited to):

Children

Elderly

Pregnant of lactating women

Patients with relevant co-morbidity such as inical signifi nt renal, hepatic or cardiac impairment

Patients with disease severity differ t from that stud d in clinical trials

Sub-populations with genetic poly orphisms

Patients of different ethnic orig s

## 1.4 Post authorisa ion experience

### *1.4.1. <Project d post-au horisation usage data>*

For the init l EU RMP, or when seeking a significant change to the indication, provide details on proj t d pattern, estimated population drug usage over time, place in treatment and market position.

### *1.4.2. <Actual post-authorisation usage data>*

F updates to the EU-RMP, specific reference should be made to how the realised pattern of exposures has differed from that predicted, including off label use.

### *1.4.3. <Regulatory action taken>*

For updates to the EU-RMP only, please list regulatory action taken (worldwide cumulative table)

| Issue | Country | Action taken | Date |
|---|---|---|---|
| Issue 1 | Country 1 | Action 1 | Date 1 |
| | Country 2 etc | Action 2 etc | Date 2 etc |
| Issue 2 etc | Country 1 etc | | |

# 1.5 Adverse events/Adverse reactions

## *1.5.1. Newly identified safety concerns (since EU-RMP last submitted*

| |
|---|
| **Safety concern 1** |
| Details |
| Source |
| Implications for product literature |
| New studies proposed in pharmacovigilance plan? Yes/No |
| New risk minimisation actions proposed? Yes/No |
| **Safety concern 2 etc** |

## *1.5.2. Details of important identified and potential ris s (including newly identified)*

For each important identified and potential risk prov de the following if available:

| | |
|---|---|
| Identified Risk <> | MedDRA PT terms |
| Seriousness/outcomes | <tabulate the istribution of outcom e.g. % fatal, % recovered/with/without treatment e elae, % not recover % hospitalised etc> |
| Severity and nature of risk | <e.g. tabula rades of severity where available> |
| Frequency with 95 % CI | the guide section 4.5.2.3: give relative and excess (over placebo or compa r) as incid e rates and incidence risk for populations:<br>1) ndomised blinded trial population only<br>) all clinic rial populations (including open extension)<br>3) miological studies stratified by indication<br>Where there are clear differences in rates between populations, this should be discussed> |
| Background incide /prevalence | Background incidence/prevalence in the target population(s) |
| Risk groups or risk fact | <describe use, dose, time and susceptibility data or other factors where available. Cumulative hazard function may be provided> |
| Potential me nisms | <describe> |
| Preventability | <provide data on predictability or preventability of ADR> |
| P ublic health impact of safety ncern | <describe or enumerate if possible, using e.g. Numbers Needed to Harm and/or expected number of patients affected, hospitalisations, fatalities given in the predicted population use> |
| Evidence urce | <identify and cross refer to supporting data in CTD or annex data> or PM clinical trials, safety studies, pharmacoepidemiological studies, PSUR, other safety reports etc. |
| Regulatory action taken | <country, type of action> |

## 1.6 Identified and potential interactions with other medicinal products, food and other substances

For each important interaction, provide the following:

| | |
|---|---|
| Interacting substance | < > |
| Effect of interaction (including MedDRA terms if appropriate) | |
| Evidence source | < > |
| Possible mechanisms | < > |
| Potential health risk | < > |
| Discussion | |

## 1.7 Epidemiology of the indication(s) and imp tant adverse events

***1.7.1.*** *For each indication, discuss the ncidence, prev lence, mortality and demographic profile of the target populatio*

| | |
|---|---|
| Indication/target population | < > |
| Incidence of target indication | < > (note if specific inter-country variation is known) |
| Prevalence of target indication | < > |
| Mortality in target indication | < > |
| Potential health risk | < > (note if specific inter-country variation is known) |
| Demographic profil of target p ulation | <Provide age sex distribution> |

***1.7.2.*** *F r each indication, discuss the important co-morbidity in the target population*

| | |
|---|---|
| Indi /target population | List important co-morbidity in the target population.<br>*For each important co-morbidity, provide incidence, prevalence and mortality in the target population and main co-prescribed medicinal products* |
| < > | < > |

***1.7.3.*** *For each identified or potential risk e.g. hepatic failure, provide the epidemiology of the condition in the target population when unexposed to the product*

| | |
|---|---|
| Identified or potential risk | < > |
| Incidence of condition | < > |
| Prevalence of condition | < > |
| Mortality of condition | < > |

## 1.8 Pharmacological class effects

Identify risks which are believed to be common to the pharmacologic class. If a risk which is common to the pharmacological class is not thought to be a safety conce n with the m dicinal product this should be justified and supporting evidence provided.

| 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 | | Product A<br>Product B<br>Product C<br>Review of dverse reactions BMJ 008: 5; 214-217 | |
| Risk 2 etc | | | |

## 1.9 Additi nal EU Requirements

***1.9.1.*** *Poten ial for o r ose*

***1.9.2.*** *Potential f transmission of infectious agents*

***1.9 3*** *Pote al for misuse for illegal purposes*

***1.9.4.*** *Potential for off-label use*

***1 5.*** *Potential for off-label-paediatric use*

## 1.10 Summary – Ongoing safety concerns

| | |
|---|---|
| Important identified risks | <.> List |
| Important potential risks | <.> List |
| Important missing information | <.> List |

# 2. PHARMACOVIGILANCE PLAN

*The pharmacovigilance plan covers the actions intended **to identify and characterise** safety concerns.It should not include actions intended to reduce or prevent risks.*

## 2.1 Routine pharmacovigilance practices

Briefly summarise the routine pharmacovigilance system. If the application is via the centra sed procedure please cross refer to the section in Module 1.

## 2.2 Summary of safety concern and planned pharma ovigilance actions

For each safety concern, provide a summary table of planned pharma ovigilance a tions. Include newly available results for updates to the pharmacovigilance pla Where o acti n beyond routine pharmacovigilance is planned, please justify.

| **Safety concern** | **Planned action(s)** |
|---|---|
| Important identified risks | < > L |
| Important potential risks | < > List |
| Important missing information | > List |

## 2.3 Detailed ction lan for specific safety concerns

For each important id tified or otential risk or missing information, provide the following:

| **Safety c ern** | < > |
|---|---|
| Action(s) prop | < > |
| Objective f proposed action(s) | < > |
| Ration e for proposed action(s) | < > |
| Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures | < > |
| Milestones for evaluation and reporting including justification for choice of milestones | < > |

| | |
|---|---|
| Titles of protocols (Annex full study protocols and provide cross reference to position in annex 5) | < > |

## 2.4 Overview of study protocols for the pharmacovigilance plan

| Study | Protocol version | Protocol status | Planned date for submission of interim data | Planned date for submission of final data |
|---|---|---|---|---|
| | | | | |

## 2.5 For updates to the EU-RMP

| **Safety concern** | **Summary of newly available results**<br>**(attach study report as an annex and provide cross reference)** | **Implicati s of all v ilable data for saf y conce n** |
|---|---|---|
| **Important identified risks** | < > List | < |
| **Important potential risks** | < > List | < > List |
| **Important missing information** | < > List | < > List |

## 2.6 Summary of outsta ding actions, including milestones

Present list of actio to be comp eted (ongoing and planned) with milestones and timelines.

| **Actions** | **Mileston s/exposure** | **Milestones/calendar time** | **Study status** |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

# PART II

## 3. EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES

The evaluation of the need for risk minimisation activities should list all safety concer pr nted section 1.10. Evaluate and justify whether routine (ie product information, labellin and pa kaging) risk minimisation activities will be sufficient or whether additional risk inimisati n ac vities ( g. educational material or training programmes for prescribers, pharmacists nd pa nts, restr ted access programmes) will be required. If additional risk minimisation activi e are ne a risk minimisation plan should be provided (see section 4). If, for any safety c ncern, n risk minimisation activities at all are proposed this should be fully justified.

### 3.1 For each safety concern from section 1 10 provi e a summary table of planned actions

| Safety concern | Routine risk minimisati activities sufficient? | f yes, provide description of routine activity and justification |
|---|---|---|
| **Important identified risks (List)** | Yes/N | |
| **Important potential risks (List)** | s/No | |
| **Important missing in ormation (List)** | Yes/No | |

### 3.2 P tential for medication errors

MA MAHs are encouraged routinely to consider the likelihood of medication errors. In particular, hey sho d assess prior to marketing, common sources of medication errors. During the development phase a during the design of the medicinal product for marketing, the applicant needs to take into accoun potential reasons for medication error. The naming (taking into account the "Guideline on the a ptability of invented names for human medicinal products processed through the centralised procedure. CPMP/328/98"), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered.

If a product has life-threatening potential when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is

common practice to administer the product at the same time as other medicinal products given by the hazardous route.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error.

Consideration should be given to the prevention of accidental ingestion or other unintended use b children.

Medication errors identified during product development should be discussed and information o the errors, their potential cause(s) and possible remedies given. Where applicable an indicati hould e given of how these have been taken into account in the final product design.

If post marketing, it becomes apparent that adverse reactions are occurring s a resu t f medic ion errors, this topic should be discussed in the updated EU-RMP and way f limit th errors proposed.

# 4. RISK MINIMISATION PLAN

For each important identified or potential risk for which **additional** risk minimisation measures are planned, provide the following:

| | |
|---|---|
| Safety concern | |
| *Routine risk minimisation activities* (i.e. product information, labelling and packaging) | *<Short description of what will be put in the SPC, labelling etc to minimise risk e.g. warning in 4.4 that caution should be used in patients with cardiac failure etc>* |
| *Additional risk minimisation activity 1* (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes) | *Objective and rationale* |
| | *Proposed actions* |
| | *Criteria to be used to verify the ccess posed risk minimisation activity* |
| | *Proposed review riod* |
| *Additional risk minimisation activity 2 etc* | *Objective nd rationale* |
| | *Pr osed a ions* |
| | *Criteria to be used to verify the success of proposed risk minimisation activity* |
| | *Proposed review period* |

# 5. SUMMARY OF THE EU RISK MANAGEMENT PLAN

| **Safety concern** | **Proposed pharmacovigilance activities**<br><br>**(routine and additional)** | **Proposed risk minimisation activities**<br><br>**(routine and additional)** |
|---|---|---|
| Safety concern 1 | E.g.<br><br>• routine pharmacovigilance<br><br>• drug utilisation study to investigate ……. | E.g.<br><br>• contraindication in section 3 of the SPC<br><br>• warnin in secti 4 4 of the SP that… .<br><br>• E ucational m ial<br><br>Contr istribution |
| Safety concern 2 etc | | |

# 6. CONTACT PERSON FOR THIS EU-RMP

| | |
|---|---|
| Names | < > |
| Position | < > |
| Qualifica ons | < > |
| Signa e | < > |

# ANNEXES

List of annexes

| Annex No | |
|---|---|
| 1 | Interface between EU-RMP and EudraVigilance ( *to be provided in electronic format)* |
| 2 | Current (or proposed if initial EU-RMP) SPC, Package leaflet |
| 3 | Synopsis of ongoing and completed clinical trial programme |
| 4 | Synopsis of ongoing and completed pharmacoepidemiologic l study programme |
| 5 | Protocols for proposed and ongoing studies from P macovig ance Plan |
| 6 | Newly available study reports |
| 7 | Other supporting data |
| 8 | Details of proposed educational progr mme (if appli ble) |

Examples of annexes include the following:

# Annex I: Interface between EU-RMP and EudraVigilance

## *EU Risk Management Template: Data Elements to be provided in Electronic Format for Centrally Authorised Medicinal Products*

As part of the EU Risk Management Plan it is important to monitor the identified or potential risks i the context of the suspected adverse reactions reported to EudraVigilance. This applies to centr ly authorised medicinal products.

To allow the identified and potential risks to be monitored in EudraVigilance, these elements sh uld be provided electronically. A template for capturing the relevant data elements will be rovi d at t EudraVigilance website (http://eudravigilance.emea.europa.eu) to coincide with the r ease o Volume 9A in one of the following formats:

- Access Database
- Microsoft Word Macros Enabled

For centrally authorised medicinal products the completed template shou d be prov ded at the initial submission of the EU Risk Management Plan and each time th pl is up ted with regard to the data elements captured in the template.

# Annex 3: Ongoing & completed clinical trial programme

| Study | Description, Phase, Countries | Design, No of patients Follow-up | Estimated/Actual completion date |
|---|---|---|---|
| *Large outcome studies* | | | |
| Study ABC | Short description of study (1 – 2 sentences including comparator name(s)/placebo)<br><br>Phase III<br><br>Germany, USA, Chile | Double-blind 4000<br><br>1 year | Jan 2005 |
| Study DEF | Etc | Double-blind 2000<br><br>1 year | F 2008 |
| *Further safety/efficacy studies of XYZ* | | | |
| Study GHI | Etc | Double-blind 1 00<br><br>26 w ks | Ma h 2005 |
| Study JKL | Etc | Ope l l 2000<br><br>48 weeks | Nov 2005 |
| *Studies in special subgroups* | | | |
| Study MNO | Etc | Open-label 1000<br><br>12 weeks | Feb 2005 |
| *Paediatric studies* | | | |
| Study PQR | Etc | Open-label 500<br><br>48 weeks | Feb 2005 |

# Annex 4: Pharmacoepidemiological programme

| Study | Description | Study designs<br><br>No of patients<br><br>Duration of follow-up | Estimated/actual completion date<br><br>(dates when interim and final study reports are expected) |
|---|---|---|---|
| | | | |