[insert only for CHMP adopted doc & add EMA header and footer]

Amsterdam, <insert full date>

<insert Doc. Ref.>

Committee for Medicinal Products for Human Use (CHMP)

Informed consent application in accordance with Article 10c of Directive 2001/83/EC

[Tick all that apply to this report:]

[ ]  CHMP and PRAC Rapporteurs preliminary Joint Assessment Report

[ ]  CHMP and PRAC Rapporteurs updated Joint Assessment Report

[ ]  List of Questions

[ ]  List of Outstanding Issues

<Invented name>

International non proprietary name or common name: <INN> <Common name>

Procedure no. EMEA/H/C/<XXX>

Applicant: <xxx>

This template is aimed for informed consent applications (submitted according to Article 10(c) of Directive 2001/83/EC) which only consist of a complete module 1, while reference is made to the pharmaceutical, preclinical and clinical data in modules 2, 3, 4, and 5 of the dossier of an existing marketing authorisation of a medicinal product based on an informed consent. The CHMP Rapporteur and PRAC Rapporteur should prepare a joint assessment report (the CHMP Co-Rapporteur is expected to comment within the general deadline for comments). There is no peer review for such applications.

|  |  |
| --- | --- |
| **CHMP Rapporteur:** |  |
| **PRAC Rapporteur:** |  |
| **EMA PL:** |  |
| **Start of the procedure:** |  |
| **Date of this report:** |  |
| **Deadline for Comments:** |  |

Note to the NCAs: Assessment reports and comments should be circulated **VIA EUDRALINK**. Product Shared Mailbox: product.name-xxxx@ema.europa.eu and product initial MAA dedicated mailbox: MAAxxxx@ema.europa.eu (xxxx refers to the product number EMA/H/C/xxxx) should always be copied.

**Guidance text** is in green italics. You may save/print a copy of this template with the drafting notes, then delete them all in one go:

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Drafting notes (Agency)” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

Do not change or delete the titles and the numbering style. (Add “Not applicable” if necessary)

Suggested font: Verdana 9.

Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.

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Administrative information

|  |  |
| --- | --- |
| **CHMP Rapporteur contact person:****PRAC Rapporteur contact person:****EMA Product Lead:****EMA Risk management specialist:** | <Name>Tel: Email:<Name>Tel: Email:<Name>Tel: Email:<Name>Tel: Email: |
| **Names of the CHMP Rapporteur assessors** **(internal and external):** | Quality<Name(s)>Tel: Email:Non-clinical<Name(s)>Tel: Email:Clinical<Name(s)>Tel: Email: |
| **Names of the PRAC Rapporteur assessors** **(internal and external):** | <Name(s)>Tel: Email: |

**MARKETING AUTHORISATION APPLICATION**

|  |  |
| --- | --- |
| Name of the medicinal product: |  |
| Applicant: |  |
| Active substance: |  |
| International Non-proprietary Name: |  |
| Pharmaco-therapeutic group(ATC Code): |  |
| Therapeutic indication(s): |  |
| Pharmaceutical form(s): |  |
| Strength(s): |  |
| Route(s) of administration: |  |
| Packaging: |  |
| Package size(s): |  |

**Cross-Referred MEDICINAL PRODUCT**

| Name of the medicinal product: |  |
| --- | --- |
| Marketing Authorisation Holder:  |  |
| Active substance: |  |
| International Non-proprietary Name: |  |
| Therapeutic indication(s): |  |
| Pharmaceutical form(s): |  |
| Strength(s): |  |
| Route(s) of administration: |  |
| Authorised in MS/Community:  |  |
| Date of initial MA in the EU: |  |

Declarations

This application includes an Active Substance Master File (ASMF):

[ ]  Yes

[ ]  No

[ ]  The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (eg. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received\*.

*\*If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there* would *be no need to add details below.*

Whenever the above box is un-ticked please indicate section and page where confidential information is located (including the Product Information document) here:

 List of abbreviations

1. Recommendations

Based on the review of data, the informed consent application for <product name> in the treatment of <claimed indication>,

<is considered approvable. Some points could be resolved after the marketing authorisation (see section 9. ).>

<could be approvable provided that satisfactory answers are given to the "other concerns" as detailed in the List of Questions/List of Outstanding issues. Failure to resolve other concerns may render the application not approvable>. <In addition, recommendations are made for conditions for marketing authorisation and product information (see section 9. ).> <However, the answers to the "other concerns" may affect the final product information and/or other conditions for the marketing authorisation.>

<is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions/List of Outstanding issues.>

<In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions/List of Outstanding issues.>

<The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:>

1. Executive summary

The section should be concise and aligned as much as possible with that of the cross-referred medicinal product. Attention should be paid not to include information from the cross-referred medicinal product’s executive summary which may now be out of date.

* + 1. Disease or condition
* State the claimed the therapeutic indication.
	+ 1. Epidemiology <and risk factors, screening tools/prevention>
* Shortly describe the epidemiology of the disease (e.g., incidence, mortality).
	+ 1. <Biologic features><Aetiology and pathogenesis>
* Focus on what is relevant for the scientific assessment (e.g., pathophysiology relevant for mechanism of action).
	+ 1. Clinical presentation, diagnosis <and stage/prognosis>
* Be as specific as possible to the claimed therapeutic indication (avoid high-level textbook introduction to a particular disease).
	+ 1. Management
* Describe aims and main methods of treatment, incl. surgery, medical therapy, etc. Refer to clinical guidelines and other published references.
* Describe the unmet medical need.

| Notes |
| --- |
| The checklist above (for example “❑ Describe the unmet medical need.”) is provided for guidance during drafting of the report - please delete the checklist from the final report.In some situations, and therapeutic areas, deviation from the recommended content and structure is necessary (e.g., vaccines, radio-pharmaceutical precursors, analogues, bio-similar medicinal products, generic medicinal products). For additional guidance on content and style and an example, see the D80 assessment report - Overview & D120 LOQ template with guidance. |

* 1. About the product

Summarise the relevant details of the medicinal product, including its active substance, mode of action, and pharmacological classification. State the indication(s), strength(s) and pharmaceutical form(s) applied for. State if the informed consent application covers all the indications, strengths and pharmaceutical forms of the cross-referred medicinal product.

Provide recommendation for use (including a possible risk management strategy) and posology.

Special pharmaceutical aspects, if any, e.g. novel delivery system, gene therapy etc.

* 1. Compliance with GLP, GMP, GCP

*Elaborate as appropriate on the Applicant’s claims of compliance with GMP, GLP and GCP. No request for inspection is expected as no new quality, non-clinical and clinical data are expected with such legal basis.*

* 1. Type of application and other comments on the submitted dossier
		1. Legal basis: article 10(c) of Directive 2001/83/EC, as amended

<Invented name> is submitted as an informed consent application of <cross-referred medicinal product>. <In addition, <invented name> is a duplicate of <cross-referred medicinal product>.>

* + 1. <Conditional marketing authorisation>

<Cross-referred product invented name> has been granted a <conditional> marketing authorisation subject to the following specific obligation(s):

<Specific obligation(s) to complete post-authorisation measures as approved for the cross-referred medicinal product.>

The Applicant of <invented name> also requested a <conditional> marketing authorisation based on the following justification:

* The benefit-risk balance is positive.
* It is likely that the applicant will be able to provide comprehensive data. {Summarise in general terms the applicant’s claim that they will provide comprehensive data}
* Unmet medical needs will be addressed, as {include the applicant’s claim on why the product will provide major therapeutic advantage over the authorised methods}. *When assessment of major therapeutic advantage over existing methods is needed, avoid the expression ‘significant benefit’, in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.*
* The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. {Summarise the applicant’s claims}>
	+ 1. <Marketing authorisation under exceptional circumstances>

<Cross-referred product invented name> has been granted a marketing authorisation <under exceptional circumstances> subject to the following specific obligation(s):

<Specific obligation(s) to complete post-authorisation measures as approved for the cross-referred medicinal product.>

The Applicant also requested a marketing authorisation <under exceptional circumstances for <invented name>.

* + 1. <Orphan designation>

Indicate if, and when the product received Orphan Drug Designation(s) related to the applied indication(s). Special consideration has to be given to orphan designated products with regard to the scope of the orphan condition in relation to the therapeutic indication claimed by the applicant (for a product to be authorised as an orphan medicinal product, the indication has to fall within the scope of the orphan designated condition).

<Product name> was designated as an orphan medicinal product EU/../../... on <date> in the following condition: <insert the orphan condition that relates to the indication in the MAA>.

* + 1. Similarity with orphan medicinal products

For all submissions, complete the following paragraph to reflect whether a similarity report was or was not submitted. If applicable, a separate AR on similarity is required (to be included as appendix).

The application <did not> contain<ed> a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. <Assessment of these claims is appended.>

* + 1. <Derogation(s) from orphan market exclusivity>

Complete the following paragraph only for submissions where claims for derogation(s) based on Art. 8.3 was/were submitted (i.e. where product is considered similar to an authorised orphan product). If applicable, separate ARs on the derogation(s) are required (to be included as appendices).

<The application contained a claim addressing the following derogation laid down in Article 8(3) of the Regulation (EC) No. 141/2000; <the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant> or < the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> <and> <the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior>. Assessment of these claims is appended.>

* + 1. Information on paediatric requirements

1) Paediatric requirements apply - Note: the Decision number below has a format P/X/XX. Do not mention the date.

<Pursuant to Article <7> <8><30> of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [insert decision number(s)] on <the agreement of a paediatric investigation plan (PIP)> OR <the granting of a (product-specific) waiver> <and> <on the granting of a class waiver>.

Only if a PIP included, i.e. not if there is a waiver:

<At the time of submission of the application, the PIP [insert decision number for the PIP eligible to the reward] was <completed> <not yet completed as some measures were deferred>.>

[Note: the following sentence to be included only in case of the PIP eligible to the reward (please check the PIP reference with the paediatric coordinator) being fully completed and a PDCO Opinion on compliance is available; compliance with a PIP not fully completed (i.e. in which case the PDCO only issues a letter and compliance report) should not be indicated here:]

<The PDCO issued an opinion on compliance for the PIP [insert decision number for the PIP eligible to the reward].>

2) Paediatric requirements do not apply: If paediatric requirements do no apply at all to the concerned application, select the statement hereafter:

<Not applicable>

1. Scientific overview and discussion
	1. Quality

<Invented name> is submitted as an informed consent application of <cross-referred product invented name> under Article 10(c) of Directive 2001/83/EC. The present application cross-refers to the up-to-date <chemical pharmaceutical> <biological> data of the original dossier of <cross-referred product invented name>, which has been assessed and authorised. The declaration submitted by the Applicant states that <invented name> possesses the same qualitative and quantitative composition in terms of active substances and <the same pharmaceutical form(s)> as <cross-referred product invented name>.

*In case the Applicant only applied for a subset of the pharmaceutical forms and/or strengths currently approved for the cross-referred product this should be specified above.*

* 1. Non clinical

<Invented name> is submitted as an informed consent application of <cross-referred product invented name> under Article 10(c) of Directive 2001/83/EC. The present application cross-refers to the up-to-date non-clinical data of the original dossier of <cross-referred product invented name>, which has been assessed and authorised.

* + 1. Environmental risk assessment

If possible, the ERA assessment should be aligned with the cross-referred medicinal product (e.g. in case of an updated ERA based on the previously submitted ERA for the cross-referred product).

**Table xxx: Summary of main study results**

|  |
| --- |
| **Substance (INN/Invented Name):** |
| **CAS-number (if available):** |
| ***PBT screening*** |  | Result | **Conclusion** |
| *Bioaccumulation potential-* log *K*ow | OECD107 or … |  | Potential PBT (Y/N) |
| ***PBT-assessment*** |
| **Parameter** | **Result relevant for conclusion** |  | **Conclusion** |
| Bioaccumulation | log *K*ow  |  | B/not B |
| BCF |  | B/not B |
| Persistence | DT50 or ready biodegradability |  | P/not P |
| Toxicity | NOEC or CMR |  | T/not T |
| **PBT-statement :** | The compound is not considered as PBT nor vPvBThe compound is considered as vPvBThe compound is considered as PBT |
| ***Phase I***  |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC surfacewater , default or refined (e.g. prevalence, literature) |  | μg/L | > 0.01 threshold (Y/N) |
| Other concerns (e.g. chemical class) |  |  | (Y/N) |
| ***Phase II Physical-chemical properties and fate*** |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 or … | *K*oc = | List all values |
| Ready Biodegradability Test | OECD 301 |  |  |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | DT50, water =DT50, sediment =DT50, whole system =% shifting to sediment = | Not required if readily biodegradable |
| ***Phase IIa Effect studies***  |
| **Study type**  | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species*  | OECD 201 | NOEC |  | µg/L | species |
| *Daphnia* sp*.* Reproduction Test  | OECD 211 | NOEC |  | µg/L |  |
| Fish, Early Life Stage Toxicity Test/*Species*  | OECD 210 | NOEC |  | µg/L | species |
| Activated Sludge, Respiration Inhibition Test  | OECD 209 | EC |  | µg/L |  |
| ***Phase IIb Studies*** |
| Bioaccumulation | OECD 305 | BCF |  | L/kg | %lipids: |
| Aerobic and anaerobic transformation in soil | OECD 307 | DT50%CO2 |  |  | for all 4 soils |
| Soil Micro organisms: Nitrogen Transformation Test | OECD 216 | %effect |  | mg/kg |  |
| Terrestrial Plants, Growth Test/*Species* | OECD 208 | NOEC |  | mg/kg |  |
| Earthworm, Acute Toxicity Tests | OECD 207 | NOEC |  | mg/kg |  |
| Collembola, Reproduction Test | ISO 11267 | NOEC |  | mg/kg |  |
| Sediment dwelling organism  |  | NOEC |  | mg/kg | species |

* + 1. Conclusion

<The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, <active substance> is not expected to pose a risk to the environment.

<Active substance> PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

<Active substance> is already used in existing marketed products and no significant increase in environmental exposure is anticipated [based on justification].

Therefore <active substance> is not expected to pose a risk to the environment.

<Active substance> is not a PBT substance or if PBT add a specific conclusion according to the PBT assessment.

- Considering the above data, <active substance> is not expected to pose a risk to the environment.

- Considering the above data, <active substance> should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

<As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of <active substance> to the environment.> <See list of questions/outstanding issues)>.

* 1. Clinical

<Invented name> is submitted as an informed consent application of <cross-referred product invented name> under Article 10(c) of Directive 2001/83/EC. The present application cross-refers to the up-to-date clinical data of the original dossier of <cross-referred product invented name>, which has been assessed and authorised.

* 1. Risk management plan

The CHMP rapporteur should assess the safety specification within the RMP. The PRAC Rapporteur should assess the pharmacovigilance plan and the risk minimisation measures.

The RMP should be the same as the RMP of the cross-referred medicinal product, if existing. Any deviation should be discussed and justified.

RMP version <XXX> was submitted.

[ ]  The RMP is in line with the approved EU-RMP version <X> of the cross-referred medicinal product.

OR

[ ]  In order to bring the RMP in line with the approved EU-RMP version <X> of the cross-referred medicinal product, the request(s) in the LoQ/LoOI must be implemented.

[Please include the requests in the LoQ/LoOI and tick option 1 instead when implemented.]

OR

[ ]  As the cross-referred medicinal product does not have an approved EU-RMP, or the applied product differs from the cross-referred product in terms of <dose/presentation/strength/formulation> with implications for risk management, the RMP is assessed in the following.

[Only in this case, the PRAC D94 Rapporteur assessment report template should be used at D94, and the following sections should not be completed in the preliminary JAR but in all later JARs.]

* + 1. Safety Specification

[To be filled in by the CHMP Rapporteur and updated throughout the procedure, considering all the comments and submissions.]

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

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

* + 1. Discussion of the safety specification

[Comment on whether the applicant’s proposal for the safety specification is adequate, also based on the assessment of any responses. State specifically if a safety concern needs to be added, removed, or changed.

Please specifically address the need to modify the proposed summary of safety concerns in the RMP.

Please flag to the PRAC Rapporteur any issue and concern that were identified during the assessment of the dossier that could impact the prospective aspects of the Risk Management Plan; i.e. the pharmacovigilance plan or the risk minimisation measures.

**For each AR version, this section should be updated** considering all comments (from the CHMP Co-Rapporteur, the PRAC rapporteur, Member States, EMA…)]

* + 1. Conclusions on the safety specification

Having considered the data in the safety specification,

<It is agreed that the safety concerns listed by the applicant are appropriate>

or

<It is considered that the following issues should be addressed :>

<It is considered that> <should also be <a> safety concern(s)>

<It is considered that the following should not be <a> safety concern(s)>

[If the second option is chosen, the issues to be addressed must be included in the LOQ]

* + 1. Pharmacovigilance Plan

[The PRAC rapporteur should complete this section and **update it throughout the procedure, as needed.**]

* + - 1. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

<None> *or summarise*

* + - 1. Summary of planned additional PhV activities

[ ]  No additional PhV activities.

or

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

| Study (study short name, and title)Status (planned/on-going) | Summary of objectives | Safety concerns addressed | Milestones (required by regulators) | Due dates |
| --- | --- | --- | --- | --- |
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation(key to benefit risk) |
|  |  |  |  |  |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk) |
|  |  |  |  |  |
| **Category 3** - Required additional pharmacovigilance activities(by the competent authority) |
|  |  |  |  |  |

[Please make sure all on-going and planned categories 1-3 safety studies included in the Pharmacovigilance Plan are listed above.

The applicant should provide information on the study design (interventional/noninterventional, controlled/uncontrolled, blinded/open-label, etc.), study population, clear milestones and due dates, submission of interim results or other intermediate milestones, if requested.

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

* + 1. Discussion of the PhV Plan

[Within this section, the PRAC rapporteur should comment on whether the applicant has discussed how the safety concerns from Module SVIII are proposed to be addressed within the pharmacovigilance plan and whether all areas requiring further investigation have been identified. PRAC rapporteur to comment on whether activities/activity changes proposed above, in the latest PI and by the CHMP rapporteur in the LoQ/LoOI (if any) are consistent, appropriate and proportionate to the importance of the risk proposed to be addressed and if more, less or different activities are needed.

The PRAC rapporteur should consider the following points:

* For all safety concerns identified in the safety specification, is routine PhV sufficient?
* Please assess and discuss any routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
* Are additional PhV activities required for any safety concern or for risk minimisation effectiveness evaluation? If yes, are the additional PhV activities proposed by the Applicant appropriate, clearly defined and described and suitable for further identifying or characterising risks or providing missing information? Are there additional activities proposed by the PRAC rapporteur?
* Do the objectives of the activities align with the identified / potential risks / missing information / risk minimisation measure requiring confirmation, further investigation or effectiveness evaluation?

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

• Category 1 studies, i.e. those that are considered key for the benefit–risk balance, should also be included as conditions of the MA (Annex II). These are studies where confirmation of a safety concern could lead to major regulatory action including suspension or revocation of the MA.

• Category 2 studies are those imposed as specific obligations in the context of a conditional MA or MA under exceptional conditions (Annex II).

• Category 3 studies: These PASSs may include trials or studies which are already on-going (e.g. from clinical trials assessing a safety concern where the activity would be to provide a report) or be planned where the activity is to conduct the study to assess a safety concern. Category 3 studies/activities would include studies or activities requested by another Regulatory authority where the results are required to assess a safety concern. Studies which have been specifically requested by the CHMP/PRAC (which are not conditions of the MA) or which may be suggested by the applicant to investigate a safety concern should also be included here. Studies to measure the effectiveness of risk minimisation measures would also normally fall into this category.]

* + 1. Conclusions on the PhV Plan

The PRAC (rapporteur), having considered the data submitted, is of the following opinion:

[Choose one of the following:]

[ ]  the proposed pharmacovigilance measures are in line with the cross-referred medicinal product.

[Or if the risk minimisation measures need to be added or modified:]

[ ]  the proposed pharmacovigilance measures are not in line with the cross-referred product, as follows: <..> *[Summarise differences]*

*[In addition, choose one of the following:]*

[ ]  the proposed post-authorisation PhV plan is appropriate to identify and characterise the safety concerns of the product.

or

[ ]  the proposed post-authorisation PhV plan is not appropriate to identify and characterise the safety concerns of the product and the applicant should modify/propose PhV measures as discussed above and requested in the LoQ/LoOI. [include in the LoQ/LoOI]

The PRAC (rapporteur) also considers that

[ ]  the proposed PhV plan is sufficient to evaluate the effectiveness of any proposed risk minimisation measures.

or

[ ]  the applicant should propose (a) study/ies to evaluate the effectiveness of [state which additional risk minimisation measures should be studied and include the study request in the LoQ/LoOI].

* + 1. <Plans for post-authorisation efficacy studies>
			1. Summary of imposed Post authorisation efficacy studies

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

| **Study** (study short name and title),**Status** (planned, on-going) | **Summary of objectives** | **Efficacy uncertainties addressed** | **Milestones** | **Due Date** |
| --- | --- | --- | --- | --- |
| Efficacy studies which are conditions of the marketing authorisation  |
|  |  |  |  |  |
| Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances |
|  |  |  |  |  |

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

* + 1. Risk minimisation measures
			1. Routine risk minimisation measures

[The PRAC rapporteur should comment, if needed]

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

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

* + 1. Discussion of the risk minimisation measures

[PRAC rap. to comment, also on other risk minimisation measures for RMP safety concerns in the latest PI and mock-ups or requested by the CHMP rapporteur in the LoQ/LoOI/PI.

Additional risk minimisation measures should only be included in the RMP if the proposed measures are necessary for the safe and effective use of the product. Request the applicant to remove any items which do not meet this criterion.]

[Please update this section in each AR version as needed.]

* + 1. <Conclusions on the risk minimisation measures>

The PRAC (rapporteur) having considered the data submitted is of the following opinions:

[Choose one of the following:]

[ ]  the proposed risk minimisation measures are in line with the cross-referred medicinal product.

[Or if the risk minimisation measures need to be added or modified:]

[ ]  the proposed risk minimisation measures are not in line with the cross-referred product, as follows:

<..> *[Summarise differences]*

*[In addition, choose one of the following:]*

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

*[Or if risk minimisation measures (either routine or additional) need to be added or modified:]*

[ ]  the proposed risk minimisation measures are not appropriate to minimise the risks of the product and need to be changed as discussed above and requested in the LoQ/LoOI *[include requests in the LoQ/LoOI/ PI with track-changes and if applicable that the applicant should propose risk minimisation evaluation activities for these measures].*

* + 1. Summary of the risk management plan

[This section should be carefully reviewed and updated throughout the procedure. RMP summaries for RMPs using Rev 2 of the template are published]

<The public summary of the RMP < may require><does not require> revision. >

* + 1. <PRAC Outcome>

[If applicable, the outcome of the PRAC plenary discussion should be added in this section.]

* + 1. <Conclusion on the RMP>

[Prior to circulation of the draft LoQ/LoOI: choose one of the following options, based on the latest assessment report version.

[A) If the RMP is acceptable:

The CHMP considered that the risk management plan version <X> is acceptable. <In addition, minor revisions were recommended to be taken into account with the next RMP update>.

[B) If the RMP could be acceptable with revisions required before opinion.

The CHMP considered that the risk management plan version <X> could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

[C) If the RMP is not acceptable.]

The CHMP considered that the risk management plan version <X> is not acceptable. Details are provided in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

* 1. Pharmacovigilance
		1. Pharmacovigilance system

<It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time.><See list of questions/outstanding issues>.

<Having considered the data submitted in the application, a pre-authorisation pharmacovigilance inspection is required>.

* + 1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1. Overall conclusion and benefit-risk assessment

This application for <invented name> is based on an informed consent to use the pharmaceutical, non-clinical and clinical documentation contained in the marketing authorisation of <cross-referred medicinal product invented name>, as complemented by administrative and prescribing information. <The applicant requested authorisation for {describe difference to cross-referred product, i.e. fewer indications, pharmaceutical forms, strengths}.>

If the application could be approvable or is not approvable:

<The benefit-risk balance for <invented name> is <currently> <negative> due to {summarise main reasons}. The aspects that are currently outstanding are outlined in the LoQ/LoOI.>

If the benefit-risk balance is positive:

<Taking into account the assessment of data previously undertaken for <cross-referred medicinal product>, the benefit-risk balance for <invented name> is considered positive.

In case of a conditional marketing authorisation has been proposed or requested:

<<At the time of this report <cross-referred medicinal product> was approved subject to a conditional marketing authorisation, as comprehensive data on the product were not available. Consequently, given that the present application for <invented name> cross-refers to the pharmaceutical, non-clinical and clinical documentation of <cross-referred medicinal product invented name>,> <a> <A> conditional marketing authorisation was <requested by the applicant in the initial submission> <proposed by the CHMP during the assessment, after having consulted the applicant> .>

In case a conditional marketing authorisation is recommended [select text as applicable, at least one of the options must apply]:

<The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the <treatment> <prevention> <medical diagnosis> of a <seriously debilitating> <life-threatening> disease. <In addition, the product<is to be used in emergency situations in response to public health threats duly recognised by the <World Health Organisation> <EU>> <and> <is designated as an orphan medicinal product>>. Include corresponding discussion to support life-threatening or seriously debilitating nature of the disease.

It is considered that the product fulfils the requirements for a conditional marketing authorisation:

* The benefit-risk balance is positive, as discussed.
* It is likely that the applicant will be able to provide comprehensive data. {Summarise the studies to be conducted and why they are considered feasible. State if all specific obligations are in line with cross-referred product (and based on the same studies or not), substantiate any differences.}
* Unmet medical needs will be addressed, as {include detailed discussion why there are no satisfactory methods authorised at all, or why the product will provide major therapeutic advantage over the authorised methods. Discuss also the authorised cross-referred product. *When assessment of major therapeutic advantage over existing methods is needed, avoid the expression ‘significant benefit’, in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.*}.
* The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.>

{Summarise the reasons for this conclusion}

In case a conditional marketing authorisation is not recommended [select text as applicable, at least one of the options must apply]:

<It is considered that the product does not fall under the scope of a conditional marketing authorisation as it is not intended for the treatment, prevention or medical diagnosis of a seriously debilitating or life-threatening disease.> <The product is not recommended for a conditional marketing authorisation as <the benefit-risk balance is negative (as discussed)>, <the applicant is unlikely to be able to provide comprehensive data after authorisation>, <it has not been demonstrated that the product will address an unmet medical need>, <and> <the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required>. All scientific arguments of the applicant should be discussed. For reasons of (a) comprehensive data unlikely to be generated post-authorisation, (b) not addressing unmet medical need and (c) benefits of immediate availability not outweigh the risks, include here corresponding discussion.

***<Marketing authorisation under exceptional circumstances>***

It is not expected that fulfilling the criteria for approval under exceptional circumstances would differ between the informed consent application and the cross-referred product. In exceptional where this is the case, the template wording needs to be adjusted.

At the time of this report <cross-referred medicinal product> was approved subject to a marketing authorisation under exceptional circumstances, as comprehensive data on the product were not available. Consequently, given that the present application for <invented name> cross-refers to the pharmaceutical, non-clinical and clinical documentation of <cross-referred medicinal product invented name>, a marketing authorisation under exceptional circumstances was <requested by the applicant in the initial submission> <proposed by the CHMP during the assessment, after having consulted the applicant>.

To be aligned with cross-referred product

IF THE PRODUCT IS APPROVABLE:

It is considered that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because <the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence> <in the present state of scientific knowledge, comprehensive information cannot be provided> <it would be contrary to generally accepted principles of medical ethics to collect such information>.

{Include corresponding discussion on this conclusion.}Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

IF THE PRODUCT IS NOT APPROVABLE:

It is considered that the absence of comprehensive data cannot be addressed by considering the benefit-risk balance in the context of a marketing authorisation under exceptional circumstances, as the applicant has not sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use. {Include discussion why arguments of the applicant are not supported.>

* 1. Conclusions

The overall benefit-risk balance of <name of product> <is positive subject to the conditions stated in section 9. ><is negative.>

1. <<Draft> CHMP List of questions>

Definitions of questions/issues:

“Major objections”, preclude a recommendation for marketing authorisation. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

“Other concerns”, may affect the proposed conditions for marketing authorisation and product information. For example, if there are no data in renally impaired patients, new data may resolve this question whereas lack of such data may lead to amendments in the SPC/follow-up measures. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

All issues identified should be asked to the company in order to resolve them before the opinion. No Post-Approval Commitments should be proposed at this phase of the assessment.

See also edits in attached product information.

* 1. Major objection(s)
	2. Other concern(s)

<To facilitate the assessment, the applicant is requested to submit clean and to the last submitted file track-changed updated RMP versions with a new version number in the same eCTD leaves as any current versions, as well as a clean working document including annexes 2 through 8 in Word.>

<The applicant should update Part VI “Summary of the risk management plan”, in line with the issues raised for other parts of the RMP and the PI.>

1. <Assessment of the responses to the list of questions>
	1. Major objections

Question

Summary of the Applicant’s Response

Assessment of the Applicant’s response

Conclusion

* 1. Other concerns

Question

Summary of the Applicant’s Response

Assessment of the Applicant’s response

Conclusion

1. <<Draft> CHMP List of outstanding issues to be addressed in an oral explanation and/or in writing>

See also edits in attached product information.

* 1. Major objection(s)
	2. Other concern(s)

<To facilitate the assessment, the applicant is requested to submit clean and to the last submitted file track-changed updated RMP versions with a new version number in the same eCTD leaves as any current versions, as well as a clean working document including annexes 2 through 8 in Word.>

<The applicant should update Part VI “Summary of the risk management plan”, in line with the issues raised for other parts of the RMP and the PI.>

1. <Assessment of the responses to the List of outstanding issues>
	1. Major objections

Question

Summary of the Applicant’s Response

Assessment of the Applicant’s response

Conclusion

* 1. Other concerns

Question

Summary of the Applicant’s Response

Assessment of the Applicant’s response

Conclusion

1. Recommended conditions for marketing authorisation and product information in case of a positive opinion

In case of major objections, inclusion of the following sentence may be considered:

<In view of the major objections it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SmPC, Annex II, labelling, PL). The assessment of the user consultation or of the justification for not having them and any above risk minimisation questions should however be addressed.>

* 1. Conditions for the marketing authorisation

[For example legal status, conditional marketing authorisation, exceptional circumstances/specific obligations and other post-authorisation measures, details of additional risk minimisation measures.

The (co)rapporteurs should review and comment on the draft Annex II, as proposed by the applicant, in the Product Information document.]

See attached edited annex II and LoQ/LoOI above.

* 1. <Proposed list of post-authorisation measures>

[This table should be reserved to include post-authorisation measures that are part of the marketing authorisation, such as (specific) obligations (annex II) and additional PK, efficacy and safety studies that have arisen based on the assessment of the data (non-clinical and clinical).]

<The proposed post-authorisation measures are subject to assessment of responses to the List of outstanding issues:>

| **Post-authorisation measure** | **Clas.** \* | **Motivation** | **Final report** |
| --- | --- | --- | --- |
| Proposed post-authorisation measure and study type: | \*: | Motivation/Background information on measure: | Due date: |
| 1. |  |  |  |
| 2. |  |  |  |
| 3. |  |  |  |
| 4. |  |  |  |

\* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other required studies reflected only in the RMP (PASS)

<Proposed list of recommendations>

| **Description of recommendation** |
| --- |
|  |
|  |

* 1. Additional monitoring

[To be completed by the PRAC rapporteur]

Complete under the assumption that the application will be approved. Ensure the end of RMP part I is aligned and that the PI contains or does not contain the black triangle, as applicable. If needed, add a respective request to your proposed LoQ/LoOI/attached track-changed PI.

The reason(s) should be identical to that of the cross-referred product. Please refer to the latest published version of list of medicinal products under additional monitoring: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852>

Pursuant to Article 23(1) of Regulation No (EU) 726/2004 (REG), Invented name (INN) <is included in> <is not included in> the additional monitoring list for the following reasons <include reason(s)>.

If this product is included in the additional monitoring list, the summary of product characteristics and the package leaflet includes the following statement "This medicinal product is subject to additional monitoring, this will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions", preceded by an inverted equilateral black triangle.

* 1. Product information

The proposed product information for <invented name> is <not fully> aligned with the latest approved version of the product information of the cross-referred product <invented name of cross-referred product> <if the informed consent applications only applies to a subset of the indications, pharmaceutical forms and/or strengths add: apart from information pertaining to {excluded indication(s), pharmaceutical form(s), strength(s)}>.

* + 1. Summary of product characteristics (SmPC)

If specific comments are warranted, these should be incorporated in the complete version of the original SmPC highlighting the proposed changes. Any comments should be put in track-changes.

See attached edited product information <and the LoQ/LoOI>.

* + 1. Labelling

If specific comments are warranted, these should be incorporated in the complete version of the original labelling highlighting the proposed changes. Any comments should be put in track-changes.

See attached edited product information <and the LoQ/LoOI>.

* + 1. Package leaflet (PL)

If specific comments are warranted, these should be incorporated in the complete version of the original PL highlighting the proposed changes. Any comments should be put in track-changes.

See attached edited product information <and the LoQ/LoOI>.

User consultation

[for guidance please see D80 AR Overview guidance]

Conclusion from the checklist for the review of user consultation

<Quick Response (QR) code>

<The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here: [Quick Response (QR) code](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2016/01/WC500199877.doc%22%20%5Ct%20%22_blank)).>

1. QRD checklist for the review of user testing results

**PRODUCT INFORMATION**

| Name of the medicinal product: |  |
| --- | --- |
| Name and address of the applicant: |  |
| Name of company which has performed the user testing: |  |
| Type of Marketing Authorisation Application: |  |
| Active substance: |  |
| Pharmaco-therapeutic group(ATC Code): |  |
| Therapeutic indication(s): |  |
| Orphan designation | [ ]  yes [ ]  no |
| Rapporteur |  |

- Full user testing report provided [ ]  yes [ ] no

- Focus test report provided [ ]  yes [ ] no

- Bridging form provided[[1]](#footnote-2) [ ]  yes [ ] no

[In case full user testing or focus test reports have been provided, please use the checklist for review of user testing results included in this document.]

- In case bridging form1 has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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- Is the justification for bridging acceptable? [ ]  yes [ ]  no

- Is the justification for not submitting a report acceptable? [ ]  yes [ ]  no

Reasons *\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

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1. Technical assessment

**1.1 Recruitment**

* Is the interviewed population acceptable? [ ]  yes [ ]  no

[ ]  no information

Comments/further details:

**1.2 Questionnaire**

* Is the number of questions \_\_\_\_\_\_\_ sufficient? [ ]  yes [ ]  no [ ]  no information
* Questions cover significant (safety) issues for the PL concerned? [ ]  yes [ ]  no

[ ] no information

Comments/further details:

**1.3 Time aspects**

* Is the time given to answer acceptable? [ ]  yes [ ]  no [ ]  no information
* Is the length of interview acceptable? [ ]  yes [ ]  no

[ ]  no information

Comments/further details:

**1.4 Procedural aspects**

* Rounds of testing including pilot \_\_\_\_\_\_\_ [ ]  yes [ ]  no [ ]  no information

Comments/further details:

**1.5 Interview aspects**

* Was the interview conducted in well structured/organised manner? [ ]  yes [ ]  no

 [ ]  no information

Comments/further details:

2. Evaluation of responses

**2.1 Evaluation system**

* Is the qualitative evaluation of responses acceptable? [ ]  yes [ ]  no

 [ ]  no information

* Does the evaluation methodology satisfy the minimum prerequisites? [ ]  yes [ ]  no

 [ ]  no information

Comments/further details:

**2.2 Question rating system**

* Is the quantitative evaluation of responses acceptable? [ ]  yes [ ]  no

[ ]  no information

Comments/further details:

3. Data processing

* Are data well recorded and documented? [ ]  yes [ ]  no

 [ ]  no information

Comments/further details:

4. Quality aspects

**4.1 Evaluation of diagnostic questions**

* Does the methodology follow Readability guideline Annex? [ ]  yes [ ]  no

[ ]  no information

* Overall, each and every question meets criterion of 81% correct answers (e.g. 16 out of 20 participants) [ ] yes [ ]  no

 [ ]  no information

Comments/further details:

**4.2 Evaluation of layout and design**

* Follows general design principles of Readability guideline [ ]  yes [ ]  no
* Language includes patient friendly descriptions [ ]  yes [ ]  no
* Layout navigable [ ]  yes [ ]  no
* Use of diagrams acceptable [ ]  yes [ ]  no

Comments/further details:

5. Diagnostic quality/evaluation

* Have any weaknesses of the PL been identified? [ ]  yes [ ]  no
* Have these weaknesses been addressed in the appropriate way? [ ]  yes [ ]  no

Comments/further details:

6. Conclusions

* Have the main objectives of the user testing been achieved? [ ]  yes [ ]  no
* Is the conclusion of applicant accurate? [ ] yes [ ]  no
* Overall impression of methodology [ ]  positive [ ]  negative
* Overall impressions of leaflet structure [ ]  positive [ ]  negative

**CONCLUSION/OVERVIEW**

1. Appendices
	1. CHMP Rapporteur AR on similarity dated < >
	2. CHMP Rapporteur AR on derogations dated < >
1. [QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2014/12/WC500179551.doc) [↑](#footnote-ref-2)