**Note for RMS:**

**This document contains the instructions (i.e. explanatory notes) for the “D70 AR Overview Template (empty)”. Furthermore, also instructions on the changes that should be made in the headings and/or statements when the D70 AR Overview is converted into the D120 AR Overview can be found in this document.**

**The RMS Day 120 Draft Assessment Report Overview (and every further Assessment Report Overview within the DCP) should include the information already included in the RMS Day 70 Preliminary Assessment Report Overview, updated if applicable.**

**However, some headings and statements should be amended in the RMS Day 120 Draft Assessment Report as a result of the timing in the procedure (next assessment round) and/or when an issue is completely solved. These headings and statements which should be amended are indicated below in grey. The accompanying instructions for the RMS are stated in text boxes.**

**Decentralised Procedure**

**RMS Day 70 Preliminary Assessment report**

**RMS Day 120 Draft Assessment Report**

**OVERVIEW**

**AND**

**LIST OF QUESTIONS**

**LIST OF OUTSTANDING ISSUES**

Note: “AND LIST OF OUTSTANDING ISSUES” should only be stated if there are remaining outstanding issues)

**<Invented Name>**

**<(Active Substance)>**

**AB/H/****nnnn****/{nnn}/DC**

**Applicant:**

|  |  |
| --- | --- |
| **Reference Member State** |  |
| **Start of the procedure:** |  |
| **Re-Start of the procedure:** |  |
| **Date of this report:** |  |
| **Deadline for comments:** |  |

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ADMINISTRATIVE INFORMATION

|  |  |
| --- | --- |
| **Proposed name of the medicinal product in the RMS** |  |
| **Name of the drug substance (INN name):** |  |
| **Pharmaco-therapeutic group (ATC Code):** |  |
| **Pharmaceutical form(s) and strength(s):** |  |
| **Reference Number(s) for the Decentralised Procedure** |  |
| **Reference Member State:** |  |
| **Concerned Member States:** |  |
| **Legal basis of application:** |  |
| **Applicant (name and address)** |  |
| **Names and addresses of all manufacturer(s) responsible for batch release in the EEA** |  |
| **Names and addresses of all manufacturer(s) of the medicinal products** | *please specify the activities for each manufacturer (e.g. manufacture of tablets, primary packaging, secondary packaging, batch control testing)* |
| **Names and addresses of all manufacturers of the active substance** | *If not applicable, please state N/A* |
| **Names and addresses of all ASMF holders (if different from manufacturer of active substance)** | *If not applicable, please state N/A* |
| **Names and addresses of all CEP holders (if different from manufacturer of active substance)** | *If not applicable, please state N/A* |
| **Names and addresses of contract companies used for clinical trials (CRO(s))** | *Please specify the duties performed according to contract (e.g. clinical study, bio-analysis, statistical analysis)*  *If not applicable, please state N/A* |
| **RMS contact person** | **Name**  Tel:  Email: |
| **Names of the assessors:** | **Quality**:  **Name(s)**  Tel:  Email:  **Non-clinical**:  **Name(s)**  Tel:  Email:  **Clinical**:  **Name(s)**  Tel:  Email:  **Pharmacovigilance/Risk Management Plan:**  **Name(s)**  Tel:  Email: |

# RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for <product name>, in the treatment of <indication>,

<could be approvable provided that satisfactory responses are given to the preliminary list of questions (Section V)>

<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 preliminary list of questions (Section V)>

In the D120 AR (and in every further Assessment Report Overview within the DCP), the statements above included in this section of the Day 70 RMS Day 70 Preliminary Assessment Report Overview should be replaced by one of the statements below.

Based on the review of the data and the Applicant’s response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for <product name> in the treatment of <indication>,

<is approvable provided that the applicant commits to perform a number of post authorisation follow- up measures <and specific obligations > to be reported back to the Member States within predefined timeframes.

A preliminary list of such follow-up measures <and specific obligations> are in section VI of this report>.

<could be approvable provided that satisfactory responses are given to the preliminary list of outstanding issues (Section V)> <and that the applicant commits to perform a number of post authorisation follow- up measures to be reported back to the RMS and CMS within predefined timeframes.

A preliminary list of such follow-up measures are in section VI.2 of this report>.

<is approvable under the specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC, see section VI.3.

<is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. <The details of these major objections are provided in the preliminary list of outstanding issues (Section V)>>.

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

Identify the need for expert involvement (e.g. Working Parties of the CHMP, pharmacovigilance expertise – PRAC - for risk management).

State the need for an inspection (GMP, GLP, GCP).

# EXECUTIVE SUMMARY

## Problem statement

Rationale for the product: epidemiology, main features of the disease and current therapy.

For generic application this section is not applicable.

## About the product

Mode of action.

Pharmacological classification.

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

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

## General comments on the submitted dossier

State the type of marketing authorisation application incl. reference to legal basis of the application

If appropriate, elaborate here on the key aspects of the dossier in relation with the legal basis.

State whether the active substance is considered as a new active substance or not.

For applications based on Art 10a (bibliographic applications): The document in Module 1.5.1 summarizing the grounds and evidence used for demonstrating that the constituents of the medicinal products have a well-established use with an acceptable level of safety and efficacy should be discussed here. It should be made clear as to why it is scientifically acceptable to waive certain studies that would normally be performed in-house

For applications made based on Art 10 (generics): The document in Module 1.5.2 summarizing the grounds and evidence used for demonstrating that the medicinal product is essentially similar to an authorised medicinal product should be discussed here.

In case a European Reference Product is used, the RMS should make clear whether the justification to use this product is based on their own files or based on the files submitted upon request by another Member State. The following paragraph can be used.

**<European Reference Product (ERP)**

A European Reference Product is used in <RMS> <and> <CMS XX>: [Name, strength, pharmaceutical form, MAH], registered in <YY>.

<The justification to use this product is based on information received from <YY>> <The justification to use this product is based on RMS’s own files>.

<The ERP information received from <YY> is attached as a separate document> <The ERP information received from <YY> was circulated during validation period>.>

Indicate if no risk management plan has been submitted based on an agreement with e.g. RMS/CMDh in advance of the application. See section III.3 Clinical aspects/RMP.

Introduce and comment the clinical development programme in view of the proposed indication and posologies (if applicable).

Indicate if, and when Scientific Advice was given and if the applicant followed this.

Indicate if the applicant followed CHMP guidance documents.

Indicate availability and need for paediatric development and development in other special populations such as the elderly, male/female and ethnic groups.

Indicate if a similarity report (module 1.7.1) has been provided by the applicant. Add a summary of the content of module 1.7.1, i.e. the authorised orphan medicinal product(s), the orphan indications, the date of the granted orphan medicinal product status and the submitted comparison.

State the RMS position on similarity/non-similarity with the authorised orphan medicinal product(s) for the proposed indication(s), taking into account Article 3 of the Commission Regulation (EC) No 847/2000. The three criteria for similarity (molecular structure, mechanism of action and indications) should be addressed. If necessary (in case of potential similarity with several authorised orphan products) a separate Similarity Assessment Report can be written, in that case reference should be made to the attached RMS similarity AR.

One of the options below and, if applicable also the conclusion, should be used for this subsection.

**Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity**

<**Potential similarity with orphan medicinal products>**

<According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.>

OR

<According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: [specify EU Orphan Designation Number(s)].

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should <submit a> <update the> report on similarity (Module 1.7.1) and, if applicable, <submit> the data to support derogation from orphan market exclusivity (Module 1.7.2).>

AND/OR

<The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity is presented in the attached RMS Similarity AR.

Conclusion

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, <product name> is considered <similar><not similar> (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to <name of authorised orphan product>. <Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for <name of authorised orphan product> in the treatment of <orphan designation>, <prevents><does not prevent> the granting of the marketing authorisation of <name of product>. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.>

During the entire procedure, the applicant should check the Community Register of orphan medicinal products and, if applicable, submit and updated/new Module 1.7.1. and Module 1.7.2). If applicable, the detailed RMS assessment of similarity should be updated accordingly.

NB: The RMS should also check the Community Register of orphan medicinal products at the moment of drafting the day 120 Overview AR and any further update of the Overview AR during the entire procedure.

**If applicable:**

Complete the following paragraph only for submissions where the product was similar to an authorised orphan medicinal product(s) and claims for derogation(s) based on Art. 8.3 of Regulation (EC) No. 141/2000 was/were submitted (Module 1.7.2). Where applicable, a separate AR on the derogation(s) will have to be adopted and attached.

The text below should in that case be used for this subsection.

**<Derogation(s) from market exclusivity**

<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> or <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.>

## General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product <,except for…. Inspection of this site is needed, because……… >.

<For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.>

<For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.>

<GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.>

Elaborate as appropriate in concordance with points made in the critical assessment modules.

A specific comment should be made as to whether any inspections are needed and if so whether it is GMP, GLP and/or GCP.

Where it is considered that one or more inspections are required make a cross-reference to the detail in sections on GMP, GLP, or GCP in the related Quality, Non-Clinical, or Clinical reports.

The inspection request should be referenced in the relevant part of sections III and V of this document.

# SCIENTIFIC OVERVIEW AND DISCUSSION

This section might be compiled from the paragraphs “assessor’s overall conclusions on….” in the critical reviews. The respective paragraphs appear at the end of the relevant parts of the detailed assessment reports. These paragraphs could be effectively copied and pasted to the corresponding headings below or written directly below at the discretion of the assessor.

In any case, salient findings on each part of the critical assessment, the discussion giving the grounds for the benefit-risk assessment, the RMS recommendations, together with questions posed to the applicant, should all be clearly outlined. There should be sufficient detail to explain the major objections.

The structure is in accordance with the LoQ and Public Assessment Report structure and can thus be updated at the different stages of the review during the decentralised procedure.

The text in this chapter should be sufficiently detailed to be used for drafting the Public Assessment Report.

For generic applications:

If the SmPC is different from that of the original product, the assessment report should outline the data supporting the modifications.

Where the SmPC of the innovator product has been approved by a Commission Decision after a Referral based on Article 30 of Dir 2001/83 this SmPC should be used for products with the same active substance and pharmaceutical form, unless specified.

## Quality aspects

**Drug substance**

<The chemical-pharmaceutical documentation and Quality Overall Summary in relation to <product name> are of sufficient quality in view of the present European regulatory requirements.>

<The control tests and specifications for drug substance product are adequately drawn up.>

<Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of <..> is justified.>

**Drug Product**

<The development of the product has been described, the choice of excipients is justified and their functions explained.>

<The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on <number> batches. The batch analysis results show that the finished products meet the specifications proposed.>

<The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.>

<The proposed shelf-life of <number> months with <storage conditions to be specified> for the drug product is considered acceptable.>

Elaborate as appropriate in concordance with points made in the critical assessment module.

The following information might be added:

- General information on results of dissolution tests

- A statement whether the active ingredient and excipients used are well known and of pharmacopoeial quality.

- If applicable, a statement on EDQM certificate of suitability is given for the active substance.

## Non clinical aspects

Generic applications in general deal with existing substances. A non-clinical assessment should be performed focused on the new information. A non-clinical assessment can only be waived in those cases where the product can be regarded as well-known in both RMS and CMS and where no new preclinical data are available. However, as soon as new non-clinical data become available, e.g. regarding pregnancy and lactation, QT, etc., which may impact the SmPC, a new non-clinical assessment has to be performed.

Bibliographic applications are ‘full dossier’ applications. Non-clinical data should be discussed here. In the AR it should be indicated whether the studies/literature submitted are relevant for the medicinal product. When certain studies are not performed it should be made clear why this is scientifically justified, based upon the criteria of ‘well established medicinal use’ as outlined in Annex 1 to Directive 2001/83/EC as amended.

**Pharmacology**

**Pharmacokinetics**

**Toxicology**

**Environmental Risk Assessment (ERA)**

<Since <Product name> is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.>

OR

<Conclusion on assessment of the ERA to be included if ERA data have been submitted by the applicant.

If applicable, the results of the non-clinical main studies should be stated.

The text below can be used for this subsection.

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 vPvB  The compound is considered as vPvB  The compound is considered as PBT | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| PEC surface water, 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 Microorganisms: 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 |

*NB: In case Phase I or Phase II studies or results of specific parameters have not been submitted these tables/parameters should be deleted.*

Conclusions on studies:

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.

OR

<Active substance> PEC surface water 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.

OR

<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 minimise any potential risks to the environment.>

If applicable, the text below can be used for this subsection.

<The applicant committed to perform the following studies as follow-up measures:

*[list of tests to be performed]* >

## Clinical aspects

Generic applications:

For medicinal products with a systemic effect, the need of appropriate bioequivalence studies should be addressed here, or it should be justified when these studies were not considered relevant or necessary. The conclusions of the assessment of these studies should be summarized here.

A confidential attachment (not to be disclosed to the applicant) should state the full composition of the reference product used in the bioequivalence studies to enable the concerned Member States to compare it with that of the approved products marketed in their own countries.

If the SmPC is different from that of the original product referred to, the AR should outline the data supporting the modifications.

Bibliographic (WEU) applications (in accordance with article 10a of Directive 2001/83/EC) are ‘full dossier’ applications. Clinical data should be discussed here.

**Pharmacokinetics**

**Pharmacodynamics**

**Clinical efficacy**

**Clinical safety**

**Summary Pharmacovigilance system**

<The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's\* Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.>

OR

<The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's\* Pharmacovigilance System.

The provided summary/summaries is/are not in accordance with the legislation and needs to be updated; *e.g. the statement included in the summary of the pharmacovigilance system is only signed by the QPPV.>*

\* applicable in case the future MAH in RMS/CMSs will be different from the applicant

**Risk Management Plan**

The following introductory statement can be included

<The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to (*insert name of medicinal product*).”>

Safety specification

[Insert summary table of proposed safety concerns (Summary of safety concerns from RMP Part II: Module SVIII)].

Pharmacovigilance Plan   
<[Insert summary of the pharmacovigilance plan (On-going and planned additional pharmacovigilance activities from RMP Part III.3)]>

*OR*

<Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.>

Risk minimisation measures

<[Insert summary table of proposed risk minimisation measures (Summary table of pharmacovigilance activities and risk minimisation measures per safety concern from RMP Part V.3].>

*OR*

<Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.>

Summary of the RMP

In this paragraph the RMS should summarise the conclusion on the assessment of the RMP.

The following statements can be used:

<The submitted Risk Management Plan, version <XX> signed <date> is considered acceptable.> <The submitted Risk Management Plan, version <XX> signed <date> is not considered acceptable. See <the separate RMP AR/or Non-Clinical / Clinical AR for Generics and> List of Questions for further details.>

Once the RMP is acceptable, the statements below should be included in the final AR.

<The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

* At the request of the RMS;
* Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.>

**Periodic Safety Update Report (PSUR)**

Use the statement(s) below which are applicable to the application.

<Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

* PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
* For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
* In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

<Active substance is currently not listed in the published EURD list

<The MAH shall submit the first periodic safety update report for this product with a period of{xx} months/{xx} years (i. e. DLP of {xx} months after authorization) following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.>

<The medicinal product is authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC. No routine PSURs need to be submitted unless it is stated as a condition in the marketing authorisation. Marketing authorisation holders shall continuously check the European medicines web-portal to see if the active substance has been included in the list of Union reference dates (EURD list). If yes, the PSURs shall be submitted in accordance with the requirements set out in the EURD list.>

**Common renewal date**

Include in this subsection the proposed renewal date by the applicant. Indicate whether this is considered acceptable and, if this proposal is not acceptable, include a proposal for an (acceptable) common renewal date.

# BENEFIT RISK ASSESSMENT

Summarise main conclusions and issues from the assessment (details to be provided under main sections dealing with quality, efficacy and safety, respectively). Integrate these aspects in a discussion of the risks and benefits in defined populations.

Integrate information on non-clinical and clinical safety along with post-authorisation commitments and elaborate on any “risk management” aspects that may influence the benefit/risk assessment.

The benefit/risk assessment should also include the following aspects, if applicable (modified from CTD):

1. Compliance with CHMP guidance documents/SA?
2. Optimal dose ranges and dosage regimens.
3. Efficacy and safety in subpopulations (e.g. as defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphism).
4. Known and potential drug interactions.
5. Safety “signals” related to, e.g. carcinogenicity, teratogenicity, QT interval prolongation, or suggestions of hepatotoxicity.
6. Use of surrogate endpoints for efficacy when important toxicity exists.
7. Have all safety issues been addressed in the pharmacovigilance plan (if provided)?
8. Safe and/or effective use of the product calls for potentially difficult selection of management approaches that involve special physician expertise or patient training.
9. Have “risks and uncertainties” been taken care of in the conditions for marketing authorisation, within the product information, as follow-up measures or in a risk management plan?
10. Do data provide sufficient information for characterisation of the benefit/risk ratio of the product as compared with appropriate recognised therapy, if any? To be addressed, as appropriate.

In addition, data on children or any paediatric development plans should be addressed.

If appropriate, this section should integrate the information and the assessment of bioequivalence for generic applications. The choice of the reference product should be stated.

In this section the need for conditions under Article 21a/22 of Directive 2001/83 should also be mentioned or referred to section VI.

# LIST OF QUESTIONS as proposed by RMS

# PROPOSED LIST OF OUTSTANDING ISSUES

Definitions of questions:

**“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 the issues are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the major objections 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 SmPC/follow-up measures. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

Comments should be made on the need for paediatric development in relation to questions on the clinical development.

## Quality aspects

**Major objections**

**Drug substance**

In addition, mention if there are additional major objections on the drug substance concerning the confidential / closed part of an ASMF. These will be detailed in an annex to the main Quality Report.

**Drug product**

**Other concerns**

**Drug substance**

In addition, mention if there are additional other concerns on the drug substance concerning the confidential / closed part of an ASMF. These will be detailed in an annex to the main Quality Report.

**Drug product**

## Non clinical aspects

**Major objections**

Pharmacology

Pharmacokinetics

Toxicology

**Other concerns**

Pharmacology

Pharmacokinetics

Toxicology

## Clinical aspects

**Major objections**

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk Management Plan

**Other concerns**

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk Management Plan

# RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

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, Package Leaflet (PL), labelling texts)”.

## Legal Status

### The RMS should conclude on the proposed prescription status

## List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

In this section post approval commitments **not** falling under Article 21a or 22 should be included, e.g. as follows:

|  |  |
| --- | --- |
| **Description** | **Due date** |
|  |  |
|  |  |
|  |  |

## List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

The need for any of the conditions mentioned under article 21a, or specific obligations under article 22 could be discussed during the assessment phase of the procedure in consultation with the PRAC, if applicable/proposed by RMS/CMSs. During this consultation with the PRAC it should also be discussed whether the product should be subject to additional monitoring and therefore required to have the black symbol in their product information.

In this section conditions and specific obligations falling under Article 21a or 22 should be included.

If considered appropriate, the following conditions should be mentioned/discussed:

Risk minimisation measures including educational material

Post-authorisation safety or efficacy studies

PSUR cycle

Approval under exceptional circumstances with annual reassessment

Product subject to additional monitoring.

If applicable, the following wording (based on annex II for centrally authorised products (QRD template human product information)) should be used:

* **<Additional risk minimisation measures (including educational material)>**

The educational material should contain the following key elements:

* **<Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83>**

The MAH shall complete, within the stated timeframe, the below measures:

|  |  |
| --- | --- |
| **Description** | **Due date** |
|  |  |
|  |  |
|  |  |

* **<Specific obligation to complete post-authorisation measures for <the marketing authorisation under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC>**

<This being a marketing authorisation under exceptional circumstances and pursuant to Article 22 of Directive 2001/83/EC, the MAH shall complete, within the stated timeframe, the following measures:>

| **Description** | **Due date** |
| --- | --- |
|  |  |
|  |  |
|  |  |

## Module I – Application related comments (including product name)

**Product name**

The RMS should indicate if the proposed product name for the RMS (in annex 5.19) can be accepted by the RMS. For article 10(1) applications with a centrally authorised product as reference product, the product name in RMS and all CMS must be the same. The RMS should then indicate if all product names proposed by the applicant can be accepted.

## 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 a boxed area within the text.

## Package Leaflet (PL)

### **Package Leaflet**

If specific comments, which go beyond the SmPC, are warranted, these should be incorporated in the complete version of the original PL highlighting the proposed changes. Any comments should be put in a boxed area within the text.

### **Assessment of User Testing**

The RMS should include an assessment of user testing, if available, using the QRD Guidance and Checklist for the Review of User Testing Results. Otherwise, a comment on whether user testing is foreseen, or whether the justification for its absence is acceptable.

<Assessment of the User Testing is attached in the ‘QRD Guidance and Checklist for the Review of User Testing Results’.> or <The applicant has stated that the readability test will be performed during clock stop: The RMS agrees with this.>

## 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 a boxed area within the text.

# APPENDIX

# QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

**QRD GUIDANCE AND CHECKLIST FOR THE REVIEW**

**OF USER TESTING RESULTS**

*[Disclaimer: This guidance has been set up to provide practical information on how to evaluate user testing reports which are based on the readability testing method as described in Annex 1 of the EC Readability Guideline. This does not exclude the submission and evaluation of user testing reports based on other methods than the one outlined above, for which specific assessment guidance may be issued once experience has been gained*

*Useful links: More detailed practical guidance can be found in the following documents:*

* *EC Readability Guideline http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/2009\_01\_12\_readability\_guideline\_final.pdf*
* *“Operational procedure on Handling of “Consultation with target patient groups” on Package Leaflets (PL) for Centrally Authorised Products for Human Use http://www.emea.europa.eu/htms/human/qrd/qrdplt/27737805en.pdf* “Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test-Recommendations for Bridging” http://www.hma.eu/fileadmin/dateien/Human\_Medicines/CMD\_h\_/procedural\_guidance/Consulation\_PatientsGroups/CMDh\_100\_2007\_Rev1\_clean\_April09.pdf
* “Position paper on user testing of package leaflets” http://www.hma.eu/fileadmin/dateien/Human\_Medicines/CMD\_h\_/procedural\_guidance/Consulation\_PatientsGroups/CMDh\_234\_2011.pdf

**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):** |  |

- Full user testing report provided  yes  no

- Bridging report provided  yes  no

In case of bridging report, multiple bridging is, in principle, not acceptable. However, a maximum of 3 bridging procedures could be accepted for one product: e.g. first bridging to address the scientific content, a second one to address the device and a last one to address the layout of the PL.

- Grounds for bridging based on a sound justification:

extensions for the same route of administration

reference to test on same class of medicinal product

reference to test with same safety issues

other \_\_\_­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Is the justification for bridging acceptable?  yes  no

In case no full user testing or bridging report has been provided, a justification should be submitted.

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

The following are examples of what are not considered valid justifications for not performing User Testing:

- Administration in a hospital setting only,

- Administration by a healthcare professional only,

- Compliance with the QRD templates,

- Long established use of the product.

The assessor’s views on acceptability or not of the justification/bridging report – assessment of justification/bridging could be included here.

Reasons

*\_\_\_\_\_\_\_\_\_\_*\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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**1 TECHNICAL ASSESSMENT**

**1.1 Recruitment**

* Is the interviewed population acceptable?  yes  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Recruitment

The following points should be taken into consideration when assessing recruitment methods:

*- Is the recruitment method well defined? Is it clear that serious thought was given to the composition of the test group? (e.g. in terms of variables such as sex, age, education, experience with the medicinal product, existing knowledge of the complaint, etc.)*

*- How has the test group been recruited? Are they new users or patients, parents or carers?*

*- Is it clear how many people were involved in the test/test rounds?*

*- Is that number sufficient? (The PL should be tested in minimum 2 rounds of 10 participants each)*

**1.2 Questionnaire**

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

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Questionnaire

The following points should be taken into consideration when assessing the questionnaire*:*

*- Have the key messages for safe use been identified by the applicant*

*- Do the questions cover the key messages and the following areas:*

*=>General impressions of package leaflet;*

*=>“Diagnostic” part of PL (i.e. questions aiming to test whether the participants were able to find specific information quickly and easily in each section of the PL and to verify if they were able to understand this information correctly; the questionnaire should primarily concentrate on safety and correct use of the medicinal product and understanding of the participant to assure safe use –it must be ensured that key safety messages have been addressed);*

*=>Aspects such as design and layout of PL.*

*- Is the number of questions sufficient? (too few or too many –e.g. 12- 15)*

*- Do the questions address “wording” aspects? Can respondents easily understand the text they are reading?*

*- Do the questions provide open or pre-defined answers? Respondents should not be provided with ready-made answers, thus increasing the possibility of positive results. Questions should be open, should be ordered randomly to see how patients use the PL and should not be leading. However, it is good practice to start with an easy question to ease the participant. Questions that require self-assessment (example: in your opinion, is paragraph X clear?) should not be used. Questions that require a long list of answers to be given (example: “what are the adverse events of this medicinal product?”) should also not be used.*

**1.3 Time aspects**

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

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Time aspects

The following points should be taken into consideration when assessing the time aspects*:*

*- Is it clear how long the test lasted?*

- *Was the time given for respondents to read and answer the questions adequate? How long did the interview last? [The test should be designed in a way to last no more than 45 minutes, to avoid tiring participants]*

**1.4 Procedural aspects**

* Rounds of testing including pilot \_\_\_\_\_\_\_

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Procedural aspects

The following points should be taken into consideration when assessing the procedural aspects:

- *Is the test based on different testing rounds? (minimum two test rounds, each involving 10 participants, are required: As this is an iterative process more rounds may be required in order to satisfy the success criteria; a pilot test (including 2 to 3 persons) could precede to assure the questionnaire is understood and major gaps are precluded. The PL after changes should then be tested on 20 participants in total. However, one single testing round may also be considered sufficient and acceptable on a case-by-case basis)*

**A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants**

*- Does it make use of modification phases in-between the testing rounds in order to maximise readability?*

*- Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate.*

**1.5 Interview aspects**

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

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Interview aspects

The following points should be taken into consideration when assessing the interview aspects:

- *Are there clear instructions for the test instructor(s)? (e.g. instructions on how to get more information from the consumers test, whether or not help should be given, etc.)*

*- Do interviewers let respondents show where information on the medicinal product can be found in the leaflet?*

*- Do they ask respondents to give their answer in their own words and not to rely on memory?*

**2 EVALUATION OF RESPONSES**

**2.1 Evaluation system**

* Is the qualitative evaluation of responses acceptable?  yes  no
* Does the evaluation methodology satisfy the minimum prerequisites?  yes  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Evaluation system

The following points should be taken into consideration when assessing the evaluation system:

*- Is the assessment based on a check list covering the following 3 basic areas:*

*Whether the respondent was able:*

*⇒* ***To find*** *the information (e.g. can a respondent easily find the information on dosage?)*

*⇒* ***To understand*** *the information (e.g. can a respondent say in his/her own words what the proper dosage and the instructions for use are?)*

*⇒* ***To use*** *the information (e.g. “imagine you are in situation X and Y happens, what must you do?”)*

**2.2 Question rating system**

* Is the quantitative evaluation of responses acceptable?  yes  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Questions rating system

The following points should be taken into consideration when assessing the questions rating system:

*- How are answers evaluated? (e.g. 1= no answer, 2=wrong answer, 3=incomplete answer, 4=ambiguous answer, 5=complete and correct answer)*

**3 DATA PROCESSING**

* Are data well recorded and documented?  yes  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Data processing

The following points should be taken into consideration when assessing the data processing:

*- Is it clear how the data are recorded?*

*- Is the way in which they are recorded satisfactory?*

*- Have the data been processed satisfactorily? (e.g., is it clear how verbal assessments have been converted into graded answers?)*

*- Has the assessor been provided with the patient leaflets used during (different rounds of) testing?*

*- Are the revisions in the PL explained/justified? Is it also clear which comment from the participants were ignored and why?*

**4. QUALITY ASPECTS**

**4.1 Evaluation of diagnostic questions**

* Does the methodology follow Readability guideline Annex 1?  yes  no
* Overall, each and every question meets criterion of 81% correct answers  yes  no

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

### Guidance regarding Quality aspects

The following points should be taken into consideration when assessing the quality aspects:

*- Is the report complete?*

*- Does the report clearly distinguish between quantitative and qualitative results?*

*- Is the medicinal product and the company concerned clearly indicated?*

*- Based on EC guidelines, are “diagnostic” questions (see 1.2) scoring satisfactorily?*

*- Do respondents find the layout and design of the package leaflet satisfactory?*

*Special focus should be given to the following elements:*

*⬂ Writing style (simple language, short sentences, use of bullets)*

*⬂ Type face (font size, italics/underlining, lower/upper case)*

*⬂ Layout (spacing, white space, contrast, left justified, columns)*

*⬂ Headings (consistent location, stand out)*

*⬂ Use of colour (present, adequate contrast)*

*- Pictograms should be subject to user testing as it is well known that these can confuse patients.*

*- Do respondents encounter difficulties in locating and using correctly (if appropriate) the information provided in the PL?*

**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\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Guidance regarding Diagnostic quality/evaluation

The following points should be taken into consideration when assessing diagnostic quality/evaluation:

*- Are the results (as far as possible) related to actual passages of text?*

*- Is an attempt made to explain that readers’ problems arose because of certain characteristics of those passages (e.g. something was difficult to find because of a badly chosen heading; or a passage could not be understood because of a double negative; or specific information could not be applied properly because certain terms were unclear)?*

*- Was a second round revision carried out?*

*- Have weaknesses of the first round been clearly identified and addressed in the appropriate way? (e.g. questions that scored low led to modifications on the PL => introduction of stylistic changes to improve readability or removal of redundant and confusing information)*

*- Is it clear which passages have been revised and how and on the grounds of what observations in the first round?*

*- Is it also clear what observations were ignored in making the revision and why?*

*- Have modifications been tested and proved to improve readability?*

**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**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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### Guidance regarding Conclusions

A general view on the user testing performed and on the overall readability /quality of the PL should be provided here *[to be used in the DCP day 70/ day 120 overview assessment report as appropriate– the complete evaluation report of the user testing results should only be included as an Annex of the Day 70 or Day 120 overview assessment report, as appropriate]*

The following points should be taken into consideration when drafting the conclusions:

*Objectives:*

*1. To ensure the final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively*

*2. To assess the readability of the PL*

*3. To identify problems regarding comprehensibility and usefulness of information*

*4. To describe possible changes in the leaflet in order to improve the readability of the leaflet*

*- Does the report make it clear on what test results specific conclusions are based?*

*- Do the conclusions match the results or, given the actual results, is too favourable a picture painted?*

*- Are the conclusions clear, concise and well organised?*

*- Have the recommendations and conclusions also been incorporated in any revision of the text?*