*December 2020*

*CMDh/191/2009 Rev.5*

**Mutual Recognition Procedure**

**Renewal**

**Preliminary Renewal Assessment Report**

**<Invented Name>**

**<(Active Substance)>**

**AB/H/****{nnn}/{nnn}/R/****{nn}**

**Marketing Authorisation Holder:**

**Date:**

**Timetable**

|  |  |
| --- | --- |
| Renewal Procedure Start Date |       |
| Date of Preliminary Renewal Assessment Report (PRAR) |       |
| Deadline for Comments by CMS (day 55) |       |
| Proposed common renewal date |  |

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**ADMINISTRATIVE INFORMATION**

|  |  |
| --- | --- |
| Name of the medicinal product(s) in the RMS |       |
| INN (or common name) of the active substance(s) |       |
| Pharmaco-therapeutic group (ATC code) |       |
| Pharmaceutical form(s) and strength(s) |       |

|  |  |
| --- | --- |
| Reference Number for the Renewal Procedure |       |
| Reference Member State |  |
| Member States concerned |       |
| Names and addresses of manufacturer(s) dosage form(s) |  |
| Names and addresses of manufacturer(s) responsible for batch release in the EEA |  |

**In the Reference Member State:**

|  |  |
| --- | --- |
| Marketing authorisation holder's name and address |       |
| Marketing authorisation number |       |

|  |  |
| --- | --- |
| RMS contact person | **Name:** Tel:      Email:       |
| Names of the assessors  | **Quality:****Name(s):** Tel:      Email:      **Nonclinical:****Name(s):** Tel:      Email:      **Clinical (efficacy):****Name(s):** Tel:      Email:      **Clinical (safety):****Name(s):**Tel:      Email:       |

**RECOMMENDATION**

Based on the review of the data submitted for this renewal application, the RMS is of the opinion that the benefit/risk balance of <product name> (<INN>) <{AB}/H/{nnnn}/{nnn}/R/{nnn}> is positive.

The RMS therefore recommends the renewal of the Marketing Authorisation for <product name>,

<Provided that satisfactory responses are given to the preliminary list of questions (Section 8)>

<The RMS is also of the opinion that the renewal can be granted with unlimited validity.>

<The RMS is of the opinion that one additional five-year renewal is required on the basis of pharmacovigilance grounds and/or additional monitoring for the product should be prolonged for a further period of x year(s) (see 4.3 ‘Conclusion on Safety’).>

Conditions to Marketing Authorisation pursuant to Article 21a, 22 or 22a of Directive 2001/83/EC

*Please choose one or more of the following options and delete the ones not applicable*

[ ]  There are **no conditions** to the Marketing Authorisation.

[ ]  For the condition(s)/ to the Marketing Authorisation that have been lifted as a result of the renewal assessment, see section 6.

[ ]  For the previously agreed condition(s) to the Marketing Authorisation that remain(s) valid and is/are still outstanding, see section 6.

[ ]  For the **new condition(s)** to the Marketing Authorisation that has/have been agreed as a result of the renewal assessment, see section 6.

Or

Based on the review of the data submitted for this renewal application, the RMS is of the opinion that the benefit/risk balance of <product name> (<INN>) <{AB}/H/{nnnn}/{nnn}/R/{nnn}> is negative. The RMS therefore considers the renewal procedure for <product name> not approvable

<since "major objections" have been identified, which preclude a recommendation for renewal of the marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (see section 8.1).>

And/or

The RMS proposes to seek advice from the Pharmacovigilance Risk Assessment Committee (PRAC) as:

* The product(s) contain(s) a substance listed as subject to additional monitoring. The RMS should then specify whether additional monitoring is no longer required or whether this should be prolonged with a period of x years(s).
* An updated RMP has been submitted that requires PRAC agreement (see section 4.2 for further details)
* As a further 5-year renewal has been proposed based on pharmacovigilance grounds and/or additional monitoring for the product should be prolonged for a further period of x year(s) (see section 4.3 for further details)

And/or

The RMS proposes to seek informal advice from the PRAC as based on the assessment of the submitted safety data a new safety signal has been identified. See section 4.2 for further details)

And/or (in FRAR only)

The RMS is of the opinion that an Urgent Union Procedure (Article 107i) should be initiated as:

* the RMS considers that the authorisation should not be renewed (see section 4.3)
* the RMS considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary (see sections 4.2 and 4.3)

# SCIENTIFIC DISCUSSION

## 1 Introduction

*Provide a short introduction on the product and its indications, including a very general overview of the product usage e.g. where it is approved and how extensive its use is: X was first authorised <in < > and> in Europe on <DD Month YYYY>. In the EU, X has been marketed in <A, B, C and D> during the reporting period. It is approved in a total of x countries and available in a total of y countries worldwide. The patient treatment years/number of patients treated are estimated to have been X within the reporting period.*

*Please indicate if the product(s) contain(s) a substance listed as subject to additional monitoring*

## 2 Module 1/GMP compliance statements

*The following documents submitted should be listed especially:*

* *GMP compliance statements for all manufacturers listed in the application form beside the manufacturers of the active substance*
* *Declaration of the qualified person as regards the manufacturer of the active substance*
* *Contact person with the overall responsibility for product defects and recalls*
* *Contact person for scientific service in charge of information about the medicinal product*
* *RMP/Updated RMP or statement why no RMP or update*

*Module 1 (renewal application form) should be checked if:*

*- There are missing documents*

*- Invalid documents (e.g. GMP compliance statements is older than 3 years)*

*- The data stated in the application form are correct*

*The MAH should be requested to update the documentation/renewal application form if necessary and provide updated or missing documents.*

*The following standard texts may be used by the RMS regarding GMP compliance:*

*“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.*

*< 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 or 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.>"*

*The following text may be used by the RMS regarding GMP statement on the active substance:*

*“GMP active substance*

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

## 3 Quality

*Relevant quality issues in the past 5 years should be summarised here, as well as a discussion on all remaining post approval commitments which have not been addressed yet. See also section 6.*

*Generally the following statement can be included:*

“In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (see CMDh website http://www.hma.eu/95.html) a quality expert statement has been submitted for < product name> confirming:

- That the products are in compliance with Article 23 of Directive 2001/83/EC which obliges the MAH “…. to take account of technical and scientific progress and introduce any changes…”.

- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

There are no outstanding quality commitments” or “The remaining quality commitments have been included in section 6.”

## 4 Clinical Efficacy and Safety

####  4.1 Efficacy

*For the whole section: include a discussion on all remaining issues that are reflected in the list of post approval commitments.*

Brief discussion of the relevant studies during the period covered and their outcome with regards to clinical efficacy

*Critical review of the efficacy of the product during the past years should be made. Please mention open or new clinical studies/new commitments/literature etc relating to efficacy.*

*New efficacy data included in Clinical Overview/Addendum to Clinical Overview should be discussed.*

*Furthermore the benefit evaluation provided by the MAH in the Addendum to the Clinical Overview should be discussed*

*For generic products the following statement will generally be sufficient to include:*

“No new clinical data have become available during the period since grant of the MA/last renewal.”

####  4.2 Safety

####

*The Clinical overview/Addendum to Clinical Overview should discuss relevant safety data collected up to the time of the renewal since the granting of the original marketing authorisation / last renewal.*

*See CMDh Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (<https://www.hma.eu/human-medicines/cmdh/procedural-guidance/renewal.html> ) for further details on data to be included in the Addendum to Clinical Overview.*

*In general in this section the safety data provided in the clinical overview/Addendum to the Clinical Overview should be discussed.*

*Clinical overview/Addendum to Clinical Overview*

*Give an overview and critical assessment of the following data provided by the MAH, if applicable:*

*- The worldwide marketing approval status: overview of number of countries where the product has been approved and marketed worldwide.- actions taken for safety reasons during the period covered since the initial marketing authorisation or since the last renewal up to 90 days prior to renewal submission: description of significant actions related to safety that had a potential influence on the benefit/risk balance of the approved medicinal product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals…).*

*- Significant changes to the SmPC (e.g. safety warnings, contraindication, restriction of indication…) during the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to renewal submission), or has made changes to the reference safety information that has not yet been agreed for the registered SmPC. Meaningful differences between the CCSI and the proposals for SmPC should be stated and discussed.*

*- Estimated exposure: data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure.*

*- Data in summary tabulations: cumulative summary tabulations of serious adverse events from clinical trials as well as cumulative summary tabulations of adverse reactions from spontaneous data sources reported during the period covered since the initial marketing authorisation or since the last renewal.*

*- Summaries of significant findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as conditions and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes.*

*- Literature: review of important literature references published during the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to the renewal submission) that had a potential impact on the benefit/risk of the medicinal product.*

*- Risk evaluation: summary of any information related to important safety issues, evaluation and characterisation of risks as well as effectiveness of risk minimisation measures for the period covered since the initial marketing authorisation or since the last renewal (up to 90 days prior to the renewal submission).*

*Pharmacovigilance System Master File (PSMF)*

*The critical assessment of the impact of findings from pharmacovigilance inspections on the benefit/risk balance of the medicinal product as provided by the MAH should be discussed*

*RMP (update)*

*Update*

*Milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as conditions and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes. Any measures in regards to a Risk Management Plan, like milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as conditions and obligations of the marketing authorisation, should be reflected here.*

*Please also indicate whether advice from the PRAC should be sought on the RMP aspects*

*Overall Conclusion on safety*

*A critical review of all safety data submitted/discussed above should be made.*

####

####  4.3 Conclusion on Benefit/Risk balance

*A critical review of the benefit/risk balance provided by the MAH in the Addendum to the Clinical Overview for the approved indication(s) should be made.*

*If an additional renewal is being requested, please elaborate here.*

*The reasons for requesting an additional renewal should be clearly stated and if considered necessary by the RMS, a proposal to seek advice from the PRAC on this request for an additional renewal should be included (i.e. a request for an additional renewal based on pharmacovigilance grounds and/or need for prolongation of additional monitoring).*

*Please also indicate if advice from the PRAC should be sought for other reasons, e.g.:*

*• The product(s) contain(s) a substance listed as subject to additional monitoring. The RMS should then specify whether additional monitoring is no longer required or whether this should be prolonged with a period of x year(s).*

*• An updated RMP has been submitted that requires PRAC agreement (see section 4.2 for further details)*

*Please also indicate if the RMS proposes to seek informal advice from the PRAC as based on the assessment of the submitted safety data a new safety signal has been identified. Please clearly mention this new safety signal(s) and explain why informal advice is sought from the PRAC.*

*Please indicate if the RMS is of the opinion that an Urgent Union Procedure (Article 107i) should be initiated, as:*

*• the RMS considers that the authorisation should not be renewed*

*• the RMS considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary*

*In both cases please provide the reason for this proposal to start an Urgent Union Procedure.*

*Please indicate
- if existing conditions to the Marketing authorisation pursuant to Article 21a, 22 or 22a of Directive 2001/83/EC remain valid or can be lifted,*

*-if new conditions to the Marketing authorisation pursuant to Article 21a, 22 or 22a of Directive 2001/83/EC should be imposed,*

*or that no conditions to the Marketing authorisation are applicable.*

*Please also provide a justification, by e.g. referring to other parts of the PRAR.*

## 5 Product Information

<The MAH proposed changes to the Product Information (PI), which were reviewed during the assessment of this renewal application <(see sections 5.1/5.2 and 5.3 below and/or Annex 1 (= Present/Proposed) of this Assessment Report)>.>

<The MAH proposed no changes to the Product Information (PI) during this procedure.>

<The RMS requests <further amendments to the PI <as discussed in sections 5.1/5.2 and 5.3.>

### **5.1 Summary of Product Characteristics**

*Brief description of both the changes proposed by the MAH as well as further changes proposed by the RMS.*

*If considered appropriate by the RMS proposed changes of the SmPC requested by the RMS also* ***may*** *be incorporated in the complete version of the original SmPC highlighting the proposed changes. Any comments should then be put in a boxed area within the text. See Annex I*

### **5.2 Package leaflet**

*Brief description of both the changes proposed by the MAH as well as further changes proposed by the RMS.*

*If considered appropriate by the RMS proposed changes of the PL requested by the RMS also* ***may*** *be incorporated in the complete version of the original SmPC highlighting the proposed changes. Any comments should then be put in a boxed area within the text. See Annex I*

No changes have been proposed by the MAH

*Or*

Some changes have been proposed see annex I, including RMS comments in a boxed area within the text>

### **5.3 Labelling**

No changes have been proposed by the MAH

*Or*

Some changes have been proposed see annex I, including RMS comments in a boxed area within the text>

## 6 List of conditions/recommendations for marketing authorisation

*Include a statement regarding conditions pursuant to Article 21a, 22 or 22a of Directive 2001/83/EC and recommendations not falling under Article 21a, 22 or 22a of Directive 2001/83/EC that have been fulfilled/remain valid or conditions/commitments that can be lifted as a result of this renewal assessment.*

*Please also include in case new conditions to the Marketing authorisation e.g. additional Risk Minimisation Measures (aRMMs)/studies have been imposed during the assessment of the renewal application.*

6.1 Conditions to Marketing Authorisation pursuant to Article 21a, 22 or 22a of Directive 2001/83/EC

*Please choose one or more of the following options and delete the ones not applicable*

[ ]  There are no conditions to the Marketing Authorisation.

[ ]  The following conditions to the Marketing Authorisation have been lifted as a result of the renewal assessment:

[ ]  The following previously agreed conditions to the Marketing Authorisation remain valid and are still outstanding:

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

[ ]  The following **new conditions** to the Marketing Authorisation have been agreed as a result of the renewal assessment:

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

**6.2 Recommendations not falling under Article 21a, 22 or 22a of Directive 2001/83/EC**

*Please choose one or more of the following options and delete the ones not applicable*

Post-approval commitments:

[ ]  There are no commitments to the Marketing Authorisation.

[ ]  The following commitments to the Marketing Authorisation have been lifted as a result of the renewal assessment:

[ ]  The following previously agreed commitments to the Marketing Authorisation remain valid and are still outstanding:

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

[ ]  The following new commitments to the Marketing Authorisation have been agreed as a result of the renewal assessment:

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

## 7. OVERALL CONCLUSION AND Benefit-risk assessment

*Include here a critical review of the benefit/risk balance of the product, and conclude the section with one of the following statements, as applicable:*

<The products are still in compliance with the current requirements regarding quality. No new clinical data have become available that changed the benefit risk assessment. Also no new safety issues were identified based on spontaneous reports, literature or published studies.
Therefore the RMS is of the opinion that the renewal can be granted with unlimited validity.>

<The RMS is of the opinion that the renewal can be granted with unlimited validity.>

<The RMS is of the opinion that one additional five-year renewal is required on the basis of pharmacovigilance grounds.>

<The RMS is of the opinion that one additional five-year renewal is required on the basis of an insufficient number of patients being exposed to the medicinal product>

*In case of the requirement of one additional renewal, please elaborate here and clearly state the reasons for requesting an additional renewal with a proposal to seek advice from the PRAC, if considered necessary.*

Or

<The RMS is of the opinion that the renewal cannot be granted since "major objections" have been identified, which preclude a recommendation for renewal of the marketing authorisation at the present time.>

In case the conclusion in the FRAR is still that the renewal cannot be granted, a proposal should be included for the PRAC to start an Urgent Union Referral.

*The RMS should review whether the PSUR cycle for the active substance as specified on the EURD list is still adequate when considering findings with regard to benefits and risks within the renewal procedure. If amendment of the PSUR cycle is warranted, the RMS should request the PRAC to amend the PSUR cycle for the active substance. Appropriate justification should be provided.*

<The MAH should continue to submit PSURs in accordance with the EURD list>

Or

No routine PSURs have to be submitted for this product as it has been authorised based on article 10.1 or 10.a of Directive 2001/83/EU; see EURD list

Or

The RMS considers that based on findings with regard to benefits and risks within the renewal procedure (please specify here), the PSUR cycle should be amended: (insert proposal here). The RMS will submit a request to the PRAC accordingly.

## 8 LIST OF QUESTIONS as proposed by RMS

|  |
| --- |
| ***Questions must be divided into “major objections” and/or “other concerns”, which are defined as follow:**** ***“Major objections”, preclude a recommendation to the renewal to the term of the 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 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 by the MAH could be considered to solve the problem.* |

##  8.1. Major objections

##  8.2. Other concerns

# ANNEX I

# Proposed changes to the <SmPC>, <PL>, <Labelling> ANNOTATED with THE RMS’s comments AFTER EACH SECTION

*This annex is not mandatory, see section 5.1, 5.2 and 5.3*