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

Amsterdam, <insert full date>

<insert Doc.Ref.:>

<Committee for Medicinal Products for Human Use (CHMP)>< Committee for Advanced Therapies Medicinal Products (CAT)>

Rapporteurs Day <106\*><150><136\*> <195> Joint <CHMP><CAT> <and PRAC response> assessment report

Overview

Or <DRAFT> <CHMP><CAT>day <120\*> <180> list of outstanding issues

\*in case of accelerated assessment

<Invented name>

<Active Substance>

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

For EU-M4all, procedure number is EMEA/H/W/xx

Applicant:

[Delete this table at the time of adoption of D180 LoOI]

|  |  |
| --- | --- |
| **<CHMP><CAT> Rapporteur:**  |  |
| **<CHMP><CAT> Co-rapporteur:** |  |
| **<CHMP coordinator(s)> *to be included only for CAT procedures*** |  |
| **PRAC Rapporteur:** |  |
| **EMA PL:** |  |
| **Start of the procedure:** |  |
| **Date of this report:** |  |
| **Deadline for comments:** |  |

Note to the (Co)[Rapporteurs](https://www.ema.europa.eu/en/glossary/rapporteur): 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 print a copy of this template with the drafting note, 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.

Table of Contents

[Administrative information 6](#_Toc148624966)

[Declarations 7](#_Toc148624967)

[List of abbreviations 8](#_Toc148624968)

[1. <Joint CoRapporteur><CHMP> <CAT> Recommendation 9](#_Toc148624969)

[1.1. Questions to be posed to additional experts 9](#_Toc148624970)

[1.2. Inspection issues 9](#_Toc148624971)

[1.2.1. GMP inspection(s) 9](#_Toc148624972)

[1.2.2. GCP inspection(s) 9](#_Toc148624973)

[1.2.3. <New active substance status> 10](#_Toc148624974)

[1.3. <Additional data exclusivity /Marketing protection > 10](#_Toc148624975)

[1.4. <Similarity with authorised orphan medicinal products> 10](#_Toc148624976)

[1.5. <Derogation(s) from market exclusivity> 10](#_Toc148624977)

[2. Executive summary 11](#_Toc148624978)

[2.1. Problem statement 11](#_Toc148624979)

[2.1.1. Disease or condition 11](#_Toc148624980)

[2.1.2. Epidemiology <and risk factors, screening tools/prevention> 11](#_Toc148624981)

[2.1.3. <Biologic features><Aetiology and pathogenesis> 11](#_Toc148624982)

[2.1.4. Clinical presentation, diagnosis <and stage/prognosis> 11](#_Toc148624983)

[2.1.5. Management 11](#_Toc148624984)

[2.2. About the product 11](#_Toc148624985)

[2.3. The development programme/compliance with guidance/scientific advice 11](#_Toc148624986)

[2.4. General comments on compliance with GMP, GLP, GCP 11](#_Toc148624987)

[2.5. Type of application and other comments on the submitted dossier 11](#_Toc148624988)

[2.5.1. Legal basis 11](#_Toc148624989)

[2.5.2. <PRIME> 12](#_Toc148624990)

[2.5.3. <Accelerated assessment> 12](#_Toc148624991)

[2.5.4. <Conditional marketing authorisation> 12](#_Toc148624992)

[2.5.5. <Marketing authorisation under exceptional circumstances> 13](#_Toc148624993)

[2.5.6. <Biosimilarity> 13](#_Toc148624994)

[2.5.7. <Additional data exclusivity/ marketing protection> 13](#_Toc148624995)

[2.5.8. <New active substance status> 13](#_Toc148624996)

[2.5.9. Orphan designation 13](#_Toc148624997)

[2.5.10. Similarity with orphan medicinal products 14](#_Toc148624998)

[2.5.11. <Derogation(s) from orphan market exclusivity> 14](#_Toc148624999)

[2.5.12. <Information on paediatric requirements> 14](#_Toc148625000)

[3. Scientific overview and discussion 15](#_Toc148625001)

[3.1. Quality aspects 15](#_Toc148625002)

[3.1.1. Introduction 15](#_Toc148625003)

[3.1.2. Active Substance 15](#_Toc148625004)

[3.1.3. Finished Medicinal Product 15](#_Toc148625005)

[3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects 16](#_Toc148625006)

[3.2. Non clinical aspects 16](#_Toc148625007)

[3.2.1. Introduction 16](#_Toc148625008)

[3.2.2. Pharmacology 16](#_Toc148625009)

[3.2.3. Pharmacokinetics 16](#_Toc148625010)

[3.2.4. Toxicology 16](#_Toc148625011)

[3.2.5. Ecotoxicity/environmental risk assessment 16](#_Toc148625012)

[3.2.6. Discussion on non-clinical aspects 17](#_Toc148625013)

[3.2.7. Conclusion on non-clinical aspects 17](#_Toc148625014)

[3.3. Clinical aspects 17](#_Toc148625015)

[3.3.1. Clinical pharmacology 17](#_Toc148625016)

[3.3.2. Discussion on clinical pharmacology 17](#_Toc148625017)

[3.3.3. Conclusions on clinical pharmacology 17](#_Toc148625018)

[3.3.4. Clinical efficacy 17](#_Toc148625019)

[3.3.5. Discussion on clinical efficacy 22](#_Toc148625020)

[3.3.6. Conclusions on clinical efficacy 23](#_Toc148625021)

[3.3.7. Clinical safety 23](#_Toc148625022)

[3.3.8. Discussion on clinical safety 24](#_Toc148625023)

[3.3.9. Conclusions on clinical safety 25](#_Toc148625024)

[3.4. Risk management plan 25](#_Toc148625025)

[3.4.1. Safety Specification 25](#_Toc148625026)

[3.4.2. Pharmacovigilance Plan 26](#_Toc148625027)

[3.4.3. <Plans for post-authorisation efficacy studies > 27](#_Toc148625028)

[3.4.4. Risk minimisation measures 27](#_Toc148625029)

[3.4.5. Summary of the risk management plan 29](#_Toc148625030)

[3.4.6. <PRAC Outcome> 29](#_Toc148625032)

[3.4.7. Conclusion on the RMP 29](#_Toc148625033)

[3.5. Pharmacovigilance 29](#_Toc148625034)

[3.5.1. Pharmacovigilance system 29](#_Toc148625035)

[3.5.2. Periodic Safety Update Reports submission requirements 30](#_Toc148625036)

[4. <Non-Conformity with agreed Paediatric Investigation Plan> 31](#_Toc148625037)

[5. Benefit risk assessment 31](#_Toc148625038)

[5.1. Therapeutic Context 31](#_Toc148625039)

[5.1.1. Disease or condition 31](#_Toc148625040)

[5.1.2. Available therapies and unmet medical need 31](#_Toc148625041)

[5.1.3. Main clinical studies 31](#_Toc148625042)

[5.2. Favourable effects 31](#_Toc148625043)

[5.3. Uncertainties and limitations about favourable effects 32](#_Toc148625044)

[5.4. Unfavourable effects 32](#_Toc148625045)

[5.5. Uncertainties and limitations about unfavourable effects 32](#_Toc148625046)

[5.6. Effects Table 32](#_Toc148625047)

[5.7. Benefit-risk assessment and discussion 33](#_Toc148625048)

[5.7.1. Importance of favourable and unfavourable effects 33](#_Toc148625049)

[5.7.2. Balance of benefits and risks 34](#_Toc148625050)

[5.7.3. Additional considerations on the benefit-risk balance 34](#_Toc148625051)

[5.8. Conclusions 36](#_Toc148625052)

[6. <Biosimilarity assessment> 36](#_Toc148625053)

[6.1. Comparability exercise and indications claimed 36](#_Toc148625054)

[6.2. Results supporting biosimilarity 36](#_Toc148625055)

[6.3. Uncertainties and limitations about biosimilarity 36](#_Toc148625056)

[6.4. Discussion on biosimilarity 36](#_Toc148625057)

[6.5. Extrapolation of safety and efficacy 36](#_Toc148625058)

[6.6. Additional considerations 36](#_Toc148625059)

[6.7. Conclusions on biosimilarity and benefit risk balance 36](#_Toc148625060)

[7. List of outstanding issues to be addressed in an oral explanation and/or in writing 37](#_Toc148625061)

[7.1. Quality aspects 37](#_Toc148625062)

[7.2. Non clinical aspects 37](#_Toc148625063)

[7.3. Clinical aspects 37](#_Toc148625064)

[7.4. Risk management plan 37](#_Toc148625065)

[7.5. Pharmacovigilance 37](#_Toc148625066)

[7.6. <Orphan similarity and derogations> 37](#_Toc148625067)

[7.7. <New active substance status> 37](#_Toc148625068)

[7.8. <Additional data exclusivity /Marketing protection> 37](#_Toc148625069)

[8. Recommended conditions for marketing authorisation and product information in case of a positive opinion 37](#_Toc148625070)

[8.1. Conditions for the marketing authorisation 38](#_Toc148625071)

[8.2. Proposed list of post-authorisation measures\* 38](#_Toc148625072)

[Proposed list of recommendations: 38](#_Toc148625073)

[8.3. Other conditions 39](#_Toc148625074)

[8.4. Summary of product characteristics (SmPC) 39](#_Toc148625075)

[8.5. Additional monitoring 39](#_Toc148625076)

[8.6. Labelling 39](#_Toc148625077)

[8.7. Package leaflet (PL) 39](#_Toc148625078)

[User consultation 39](#_Toc148625079)

[Conclusion from the checklist for the review of user consultation 39](#_Toc148625080)

[<Quick Response (QR) code> 39](#_Toc148625081)

[9. Appendices *(as appropriate)* 40](#_Toc148625082)

[9.1. <Rapporteurs><CHMP><CAT> questions on the ASM (active substance manufacturer) restricted part of the DMF 40](#_Toc148625083)

[9.2. AR on New Active Substance Claim dated < > 40](#_Toc148625084)

[9.3. AR on similarity dated < > 40](#_Toc148625085)

[9.4. AR on derogations dated < > 40](#_Toc148625086)

[9.5. AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies – Article 14(11) dated < > 40](#_Toc148625087)

[9.6. AR on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication – Article 10(5) dated < > 40](#_Toc148625088)

[9.7. AR on the significant non-clinical or clinical data in relation to the claimed new indication – Article 74a dated < > 40](#_Toc148625089)

[10. QRD checklist for the review of user testing results 41](#_Toc148625090)

Administrative information

|  |  |
| --- | --- |
| **Invented name of the medicinal product:** |  |
| **INN (or common name) of the active substance(s):** |  |
| **Applicant:** |  |
| **Applied Indication(s):** |  |
| **Pharmaco-therapeutic group** **(ATC Code):** |  |
| **Pharmaceutical form(s) and strength(s):** |  |
| **<CHMP><CAT >Rapporteur contact person:****<CHMP><CAT> Co-Rapporteur contact person:**For CAT procedures:**CHMP Coordinator(s)****PRAC Rapporteur contact person:****EMA Product Lead:** | Name:Tel: Email:Name:Tel: Email:Name:Tel: EmailName:Tel: Email:>Name:Tel: Email: |
| **Names of the <CHMP><CAT> Rapporteur assessors** **(internal and external):** | **Quality:**Name(s)Tel: Email:**Non-clinical:**Name(s)Tel: Email:**Clinical :**Name(s)Tel: Email: |
| **Names of the <CHMP><CAT> Co-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:** | Name(s)Tel: Email: |

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. <Joint CoRapporteur><CHMP> <CAT> Recommendation

Based on the review of the data and the Applicant’s response to the <list of questions> <list of outstanding issues> on quality, safety, efficacy, the application for <product name>, <an orphan medicinal product> in the treatment of <claimed indication>,

<is considered approvable provided that the applicant commits to perform a number of post authorisation measures <and specific obligations> to be reported back to the <CHMP><CAT> within predefined timeframes. A list of such post-authorisation measures <and specific obligations> is in section VIII of this report><and provided that points related to the RMP are taken into account in the next update of the RMP>.

<With reference to Part II.6 of the Annex I to Directive 2001/83/EC as amended, a marketing authorisation under exceptional circumstances can be recommended since <the indication(s) for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the <quality>, <safety> and <efficacy> of the medicinal product.> <in the present state of scientific knowledge, comprehensive information on the <quality>, <safety> and <efficacy> of the medicinal product cannot be provided by the applicant.> <comprehensive information on the <quality>, <safety> and <efficacy> of the product cannot be provided because it would be contrary to generally accepted principles of medical ethics to collect such information.>

<could be approvable provided that satisfactory responses are given to the list of outstanding issues (Section VI)> <and that the applicant commits to perform a number of post authorisation measures to be reported back to the <CHMP><CAT> within predefined timeframes. A preliminary list of such post-authorisation measures is in section VIII of this report.>

<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 list of outstanding issues (Section VII).>

* 1. Questions to be posed to additional experts
	2. Inspection issues
		1. GMP inspection(s)

[For requested GMP inspections with outstanding outcome on Day 180]

<A request for GMP inspection has been adopted for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>

* + 1. GCP inspection(s)

[For requested GCP inspections with outstanding outcome on Day 180]

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>

* + 1. <New active substance status>

Based on the review of the data, it is considered that the active substance <active substance> contained in the medicinal product <product name> <is> <could be> <is not> qualified as new active substance <provided that satisfactory responses are given to the concerns as detailed in the List of Outstanding issues>. <The major objections identified, which preclude the recommendation are detailed in the List of outstanding issues.>

* 1. <Additional data exclusivity /Marketing protection >

*[Not applicable for EU-M4all]*

For applications including a new indication, for which the applicant claimed an additional year of marketing protection in accordance with Art 14(11) of Regulation (EC) No 726/2004 – new indication submitted within the 8 first years of a MA or one year of data exclusivity in accordance with Art 10(5) of Directive 2001/83/EC - new indication for a well established substance

<Taking into account the provisions of <Article 14(11) of Regulation (EC) No 726/2004> <Article 10(5) of Directive 2001/83/EC>, it <is considered> <could be considered> <is not considered> that [For Art 14(11)]<the new therapeutic indication brings significant clinical benefit in comparison with existing therapies> OR [For Art 10(5)] that <the <pre-clinical tests> <and> <clinical studies> carried out in relation to the new indication were significant> <provided that satisfactory responses are given to the concerns as detailed in the <List of outstanding issues>.<The major objections identified, which preclude the recommendation are detailed in the List of outstanding issues.>

[For applications including a legal status switch, for which the applicant claimed an additional year of data exclusivity:]

Taking into account the provisions of Article 74(a) of Directive 2001/83/EC, it is considered> <could be considered> <is not considered> that the <pre-clinical tests> <and> <clinical trials> submitted in support of the classification of {specify medicinal product name} as ‘medicinal product not subject to medical prescription’ are significant <provided that satisfactory responses are given to the concerns as detailed in the List of outstanding issues>.<The major objections identified, which preclude the recommendation are detailed in the List of outstanding issues.>

* 1. <Similarity with authorised orphan medicinal products>

It is considered that <name of product> <is> <could be> <is not> similar to <name of authorised orphan medicinal products> within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 <provided that satisfactory responses are given to the concerns as detailed in the List of outstanding issues>.

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

It is considered that pursuant to Article 8 of Regulation (EC) No. 141/2000 and <Article 3 of Commission Regulation (EC) No 847/2000> the following derogation<s> laid down in Article 8.3 of the same Regulation <apply/ies> <could apply provided that satisfactory responses are given to the concerns as detailed in the List of outstanding issues> <do/es not apply>:

<the holder of the marketing authorisation for <authorised orphan medicinal product> is unable to supply sufficient quantities of the medicinal product>

<the applicant could establish in the application that the medicinal product, although similar to <authorised orphan medicinal product>, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication>

<the holder of the marketing authorisation for <authorised orphan medicinal product> has given his consent to the applicant.>

1. Executive summary
	1. Problem statement
		1. Disease or condition
		2. Epidemiology <and risk factors, screening tools/prevention>
		3. <Biologic features><Aetiology and pathogenesis>
		4. Clinical presentation, diagnosis <and stage/prognosis>
		5. Management
	2. About the product
	3. The development programme/compliance with guidance/scientific advice
	4. General comments on compliance with GMP, GLP, GCP
	5. Type of application and other comments on the submitted dossier
		1. Legal basis

The legal basis for this application refers to:

For all submissions: Choose one among the following 5 options:

<Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

<Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well established medicinal use supported by bibliographic literature.>

<Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.>

<Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal products.>

<Article 58 of Regulation (EC) No 726/2004, - complete and independent application, by analogy to Article 8(3) of Directive 2001/83/EC.>

<Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, < (1)> < (2) point(s) (a) (b) (c) (d) (e)> - Extensions of marketing authorisations

For a grouping of extension of MA and variations:

<Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations>

* + 1. <PRIME>

Indicate if PRIME eligibility was granted – information can be found in the list of PRIME products on EMA website:

«prodname» was granted eligibility to PRIME on <date> in the following indication: <insert the indication for which PRIME was granted.

* + 1. <Accelerated assessment>

<The CHMP <and CAT><agreed> <did not agree> to the applicant’s request for an accelerated assessment as the product was <not> considered to be of major public health interest. This was based on {include summary of reasons for accepting or rejecting accelerated assessment}.>

[If the accelerated assessment is no longer appropriate the Rapporteurs/CHMP/CAT should propose to -revert to standard timetable:]<However, it is no longer appropriate to pursue accelerated assessment, as {include summary of reasons for reverting to standard timetable}.>

* + 1. <Conditional marketing authorisation>

<The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

* 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 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>

<The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation based on *{summarise the applicant’s claims}.>*

* + 1. <Biosimilarity>

[Refer to guidance and table for the RMP in the D80 Overview/D120 LOQ template]

* + 1. <Additional data exclusivity/ marketing protection>

<The applicant requested consideration of one year <data exclusivity> <marketing protection> in regards of its application for a <new indication> <for a change in the legal status classification> in accordance with <Article 10(5) of Directive 2001/83/EC> <Article 74a of Directive 2001/83/EC><Article 14(11) of Regulation (EC) 726/2004>. <Assessment of this claim is appended.>

* + 1. <New active substance status>

[This section has to be filled out in case the applicant has claimed that the compound is a new active substance, either ‘in itself’ or in comparison to a substance previously authorised as a medicinal product in the European Union.

If the initial claim for NAS by itself is changed (as not acceptable) to NAS in comparison to an AS previously authorised in the EU because of differences in safety/efficacy compared to existing AS/product, please indicate the new claim.]

<The applicant requested the active substance {*active substance*} contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.>

[or]

<The applicant requested the active substance {active substance} contained in the above medicinal product to be considered as a new active substance in comparison to {active substance} previously authorised in the European Union as {*name of the medicinal product authorised*}, as the applicant claimed that {*active substance*} differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.>

[or]

<The applicant requested the radiopharmaceutical substance *<active substance >* to be considered as a new active substance as <it is a constituent not previously authorised in a medicinal product in the European Union> <the coupling mechanism to link *<active substance>* and <the radionuclide> <the ligand> has not been authorised previously in the European Union>.>

<Assessment of this claim is appended.>

* + 1. Orphan designation

<Not Applicable.>

or

<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

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did<not> submit a critical report, addressing the possible similarity with authorised orphan medicinal products <because there is no authorised orphan medicinal product for a condition related to the proposed indication>. <Assessment of these claims is appended.>

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

* + 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

The structure of this AR is in accordance with the Day 150 AR and will be updated at the different stages of the CHMP/CAT review (Day 180/CHMP/CAT AR/EPAR) so as to constitute a self-standing document. See also the Day 80 Overview + D120 LOQ template-guidance.

It should therefore be sufficiently detailed to eventually be used for the CHMP/CAT (Withdrawal) AR and (W)EPAR and give sufficient justifications for the D180 LoOI as appropriate.

Tables and graphs to display results are encouraged.

* 1. Quality aspects
		1. Introduction

The following text may be used:

<The finished product is presented as <pharmaceutical form(s)> containing <strength(s)> of <INN> as active substance.

Other ingredients are: (include the list of excipients as described in section 6.1)

The product is available in <primary packaging as described in section 6.5 of the SmPC>.

Mention Medical Devices, if it is part of the presentation of the medicinal product.

* + 1. Active Substance
			1. General Information
			2. Manufacture, process controls and characterisation
			3. Specification, analytical procedures, reference standards, batch analysis, and container closure
			4. Stability
		2. Finished Medicinal Product
			1. Description of the product and Pharmaceutical Development
			2. Manufacture of the product and process controls
			3. Product specification, analytical procedures, batch analysis
			4. Stability of the product
			5. <Biosimilarity>
			6. Post approval change management protocol(s)
			7. Adventitious agents
			8. GMO
		3. Discussion and conclusions on chemical, pharmaceutical and biological aspects
	1. Non clinical aspects
		1. Introduction
		2. Pharmacology
			1. Primary pharmacodynamic studies
			2. Secondary pharmacodynamic studies
			3. Safety pharmacology programme
			4. Pharmacodynamic drug interactions
		3. Pharmacokinetics
		4. Toxicology
			1. Single dose toxicity
			2. Repeat dose toxicity
			3. Genotoxicity
			4. Carcinogenicity
			5. Reproductive and developmental toxicity
			6. Toxicokinetic data
			7. Local Tolerance
			8. Other toxicity studies
		5. Ecotoxicity/environmental risk assessment
		6. Discussion on non-clinical aspects

<Assessment of paediatric data on non-clinical aspects>

* + 1. Conclusion on non-clinical aspects
	1. Clinical aspects
* **Tabular overview of clinical studies**
	+ 1. Clinical pharmacology
			1. Pharmacokinetics

*Absorption*

*Distribution*

*Elimination*

*Dose proportionality and time dependencies*

*Special populations*

|  | Age 65-74(Older subjects number /total number) | Age 75-84(Older subjects number /total number) | Age 85+(Older subjects number /total number) |
| --- | --- | --- | --- |
| PK Trials |  |  |  |

*Pharmacokinetic interaction studies*

*Pharmacokinetics using human biomaterials*

* + - 1. Pharmacodynamics

***Mechanism of action***

***Primary and Secondary pharmacology***

* + 1. Discussion on clinical pharmacology
		2. Conclusions on clinical pharmacology
		3. Clinical efficacy
			1. Dose-response studies
			2. Main study(ies)

<Title of Study>

Methods

Study Participants

Treatments

Objectives

Outcomes/endpoints

Sample size

Randomisation and blinding (masking)

Statistical methods

Results

Participant flow

Randomized (n= )

Assessed for eligibility (n= )

Excluded (n= )

♦  Not meeting inclusion criteria (n= )

♦  Declined to participate (n= )

♦  Other reasons (n= )

Analysed (n= )
♦ Excluded from analysis (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Analysed (n= )
♦ Excluded from analysis (give reasons) (n= )

***Allocation***

***Analysis***

***Follow-Up***

***Enrollment***

Recruitment

Conduct of the study

Baseline data

Numbers analysed

Outcomes and estimation

Ancillary analyses

* + - 1. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the <benefit risk assessment><biosimilarity assessment> (see later sections).

**Table XXX.** Summary of efficacy for trial <trial>

| **Title:** <title> *{as indicated on the study report}* |
| --- |
| Study identifier | <code>*{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}* |
| Design | <free text>*{describe key elements of the design (cross-over, parallel, factorial, dose- escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-centre, etc.}* |
| Duration of main phase: Duration of Run-in phase: Duration of Extension phase: | <time><time> <not applicable><time> <not applicable> |
| Hypothesis | <Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify> |
| Treatments groups*{add as many rows as needed to describe the treatment groups}* | <group descriptor>*{provide abbreviation for use later in the table of the results section}* | <treatment>. <duration>, <number randomized> |
| <group descriptor> | <treatment>. <duration>, <number randomized> |
| <group descriptor> | <treatment>. <duration>, <number randomized> |
| Endpoints and definitions*{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}* | <Co->Primary endpoint | <label>*{generate abbreviation for use later in the table of the results section}* | <free text> *{provide brief description}* |
| <Secondary><other: specify> endpoint | <label> | <free text> *{provide brief description}* |
| <Secondary><other: specify> endpoint | <label> | <free text> *{provide brief description}* |
| Database lock | <date> |
| **Results and Analysis***{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}* |
| **Analysis description** | **Primary Analysis** |
| Analysis population and time point description | <Intent to treat> <Per protocol> <other: specify>*{consider adding a brief description of the definition of the population}*<time point> |
| Descriptive statistics and estimate variability | Treatment group | <group descriptor>*{as per above terminology}* | <group descriptor>*{as per above terminology}* | <group descriptor>*{as per above terminology}* |
| Number of subject | <n> | <n> | <n> |
| <endpoint>*{label as above}*(<statistic>)*{e.g. mean, median, etc}* | <point estimate> | <point estimate> | <point estimate> |
| <variability statistic>*{e.g. standard deviation, confidence interval, etc}* | <variability> | <variability> | <variability> |
| <endpoint> (<statistic>) | <point estimate> | <point estimate> | <point estimate> |
| <variability statistic> | <variability> | <variability> | <variability> |
| <endpoint> (<statistic>)<variability statistic> | <point estimate><variability> | <point estimate><variability> | <point estimate><variability> |
| Effect estimate per comparison*{add as many rows as needed to describe the relevant statistical testing performed}* | <Co->Primary endpoint | Comparison groups | <group descriptors>*{as per above terminology}* |
|  |  | <test statistic> *{e.g. difference between groups}* | <point estimate> |
|  |  | <variability statistic>*{e.g. confidence interval, etc}* | <variability> |
| P-value*{indicate statistical test used, e.g. ANOVA}* | <P-value> |
| <<Co->Primary ><Secondary><ot her: specify> endpoint*{indicate endpoint using terminology as per row “Endpoint and definitions}* | Comparison groups | <group descriptors> |
| <test statistic> | <point estimate> |
| <variability statistic> | <variability> |
| P-value | <P-value> |
| <<Co->Primary ><Secondary><ot her: specify> endpoint | Comparison groups | <group descriptors> |
| <test statistic> | <point estimate> |
| <variability statistic> | <variability> |
| P-value | <P-value> |
| Notes | <free text>*{consider amongst others the following information:** *reasons for drop-outs*
* *critical findings with regard to the analysis}*
 |
| **Analysis description** | **<Secondary analysis> <Co-primary Analysis> <Other, specify: >***{also indicate if the conduct of the analysis was pre-specified}* |
| *{repeat all the above sections for each analysis that is considered relevant}* |  |

* + - 1. Clinical studies in special populations

|  | **Age 65-74(Older subjects number /total number)** | **Age 75-84(Older subjects number /total number)** | **Age 85+(Older subjects number /total number)** |
| --- | --- | --- | --- |
| Controlled Trials |  |  |  |
| Non Controlled trials |  |  |  |

* + - 1. In vitro biomarker test for patient selection for efficacy
			2. Analysis performed across trials (pooled analyses AND meta-analysis)
			3. Supportive study(ies)
		1. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data and additional analyses

<Additional expert consultation>

<Assessment of paediatric data on clinical efficacy>

<Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances>

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations where, for a number of reasons, it does not seem possible to ever assemble a “full” dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be submitted.

* + 1. Conclusions on clinical efficacy

In case conditions for Annex II in relation to the <conditional> MA <under exceptional circumstances> have been identified, use the following statement:

<The following measures are necessary to address the missing efficacy data in the context of a <conditional> MA <under exceptional circumstances>:>

* + 1. Clinical safety
			1. Patient exposure
			2. Adverse events
			3. Serious adverse events, deaths, other significant events
			4. Laboratory findings
			5. In vitro biomarker test for patient selection for safety
			6. Safety in special populations

| **MedDRA Terms** | **Age <65****number (percentage)** | **Age 65-74****number (percentage)** | **Age 75-84****number (percentage)** | **Age 85+****number (percentage)** |
| --- | --- | --- | --- | --- |
| Total AEs |   |   |   |   |
| Serious AEs – Total |   |   |   |   |
| - Fatal |   |   |   |   |
| - Hospitalization/prolong existing hospitalization |   |   |   |   |
| - Life-threatening |   |   |   |   |
| - Disability/incapacity |   |   |   |   |
| - Other (medically significant) |   |   |   |   |
| AE leading to drop-out |   |   |   |   |
| Psychiatric disorders  |   |   |   |   |
| Nervous system disorders |   |    |   |   |
| Accidents and injuries  |   |   |   |   |
| Cardiac disorders  |   |   |   |   |
| Vascular disorders  |   |   |   |   |
| Cerebrovascular disorders  |   |   |   |   |
| Infections and infestations  |   |   |   |   |
| Anticholinergic syndrome |  |  |  |  |
| Quality of life decreased  |   |   |   |   |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures |   |   |   |   |
| <other AE appearing more frequently in older patients> |  |  |  |  |

* + - 1. Immunological events
			2. Safety related to drug-drug interactions and other interactions
			3. Discontinuation due to adverse events
			4. Post marketing experience
		1. Discussion on clinical safety

[Discuss on whether the responses to questions raised related to safety impact on the safety specification in the RMP.]

<Additional expert consultation>

<Assessment of paediatric data on clinical safety>

<Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances>>

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations where, for a number of reasons, it does not seem possible to ever assemble a “full” dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be submitted.

* + 1. Conclusions on clinical safety

[D150: Conclude on whether the responses to questions related to safety impact the safety specification in the RMP.]

[D180: Apart from the overall conclusion on safety, comment also on which safety findings should be considered for inclusion in the safety specification of the RMP (See further below).]

In case conditions for Annex II in relation to the <conditional> MA <under exceptional circumstances> have been identified, use the following statement:

<The following measures are necessary to address the missing safety data in the context of a <conditional> MA <under exceptional circumstances>:>

* 1. Risk management plan
		1. Safety Specification

Summary of safety concerns

[**At D150** the CHMP rapporteur should assess the safety specifications]

[**Prior to circulation of the Draft D180 LoOI**, the section on safety concerns should be updated by the CHMP rapporteur, considering comments from the CHMP Co-Rapporteur, PRAC, Member States, EMA...]

The applicant identified the following safety concerns in the RMP: *[Please copy table from Module SVIII Summary of the Safety Specification]*

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 based on the assessment of the responses. *State specifically if a safety concern needs to be added, removed, or changed.]*

* + - 1. Conclusions on the safety specification

Having considered the data in the safety specification

<The rapporteur agrees that the safety concerns listed by the applicant are appropriate>

*or*

<The rapporteur considers that the following issues should be addressed :>

<The rapporteur considers that> <should also be <a> safety concern(s)>

<The rapporteur considers 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 LoI]*

 [**Prior to circulation of the Draft D180 LoOI**, please update the scientific discussion on the safety specification.]

* + 1. Pharmacovigilance Plan
			1. ***<Routine pharmacovigilance activities***>

[In this section PRAC rapporteur should comment on routine pharmacovigilance activities, if needed]

* + - 1. ***<Summary of additional PhV activities>***

[Please copy RMP table III.3 (only studies of categories 1-3)]

Table Part III.3: 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)* |
|  |  |  |  |  |

[Comment on whether routine pharmacovigilance is sufficient or whether additional activities are warranted. Comment on whether proposed activity(ies) is (are) appropriate and proportionate to the importance of the risk proposed to be addressed and if additional activities are required.]

[Please update the scientific discussion on pharmacovigilance activities prior to circulation of the draft D180 LoOI.]

* + - 1. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that <routine pharmacovigilance is sufficient to identify and characterise the risks of the product.>< the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.>< the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the applicant should propose PhV studies.>

Or if nothing has been proposed

<The <applicant> should propose a post-authorisation PhV development plan.>

The PRAC Rapporteur also considered that <routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.> or < the study(ies) in the post-authorisation development plan <is><are>sufficient to monitor the effectiveness of the risk minimisation measures.> or <Applicant> should propose a study to monitor the effectiveness of [state which additional risk minimisation measures should be studied and include question in the LoI].

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

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]

* + - 1. <Summary of additional risk minimisation measures>

[Please copy table from RMP section V.3.]

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> |

[Comment on whether risk minimisation activities as proposed by the applicant are sufficient or whether additional risk minimisation measures are needed.]

[Please update the scientific discussion on the additional risk minimisation measures prior to circulation of the draft D180 LoOI.]

* + - 1. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

[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 some other risk minimisation measures (either routine or additional) need to be added]

<the proposed risk minimisation measures are not sufficient to minimise the risks of the product> and supplementary risk minimisation measures are required relating to: *[List safety concerns and ensure questions added to LoI.]*

[Or when the risks cannot be brought to a satisfactory level]

<the proposed risk minimisation measures are not sufficient to minimise the risks of the product in the proposed indication(s).>

* + 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 will now be 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, the above sections should be updated accordingly prior to circulation of the draft D180 LoI.

* + 1. Conclusion on the RMP

[Prior to circulation of the draft D180 LoOI: choose one of the following options, based on the latest assessment report version.

[A) If the RMP is acceptable:

The CHMP and PRAC 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 and PRAC 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.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

[C) If the RMP is not acceptable.]

The CHMP and PRAC 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 was not appropriate to conclude on pharmacovigilance system at this time.><See list of outstanding issues.>

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

* + 1. Periodic Safety Update Reports submission requirements

**[This section should be completed by the PRAC Rapporteur]**

**[For all medicinal products, except EU-M4all products, use one of the following options]**

[**Option 1:** If **the substance is not already included in the EURD list**, the new EURD list entry will be based on the IBD or EBD; request the applicant to indicate whether they wish to align the EBD to IBD with an additional question in the list of outstanding issues and use the following statement:]

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points.> The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. <The applicant did <not> request an alignment of the PSUR cycle with the international birth date (IBD).> <The IBD is {DD.MM.YYYY.}>

For the LOOI : <The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

[**Option 2:** If the substance is already included in the EURD list, evaluate whether the relevant entry is valid for the MAA. If the relevant entry could not be valid for the MAA (e.g. a specific entry for a particular indication/pharmaceutical form/legal basis is needed), the PRAC Rapporteur should verify if a separate entry is needed]

* [In case the already existing entry is valid for the MAA, use the following statement:]

<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.>

[In case a separate entry is needed, in addition to the already existing one, complete the following statement, providing the rationale for such addition of entry and request the applicant to clarify whether they wish to align the EBD to IBD in the list of question]

<Based on {*provide scientific reason*}, the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for {*invented name*} is needed, as it cannot follow the already existing entry for {*active substance*}. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request the alignment of the new PSUR cycle with the international birth date (IBD). {The IBD is DD.MM.YYYY.} The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.>

*For the LOQ:* <The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

[In case the already existing entry needs to be amended on the basis of the data submitted with the MAA, complete the following statement, providing the rationale for such amendment.]

<Based on {*provide scientific reason*}, the CHMP is of the opinion that the already existing entry in the EURD list for {*active substance*} needs to be amended as follows: the PSUR cycle for the medicinal product should follow a <half-yearly> <yearly> cycle. The next data lock point will be {*date*}. >

**[For EU-M4all products, use the following statement]**

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on <*date of initial scientific opinion*>.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every <*frequency*> until otherwise agreed.

1. <Non-Conformity with agreed Paediatric Investigation Plan>

<Study(ies) identifier> <is><are> not in conformity with the agreed Paediatric Investigation Plan *{insert relevant PIP decision number(s)}* as set out in Article 24 of Regulation (EC) No 1901/2006. The detailed grounds for the non-conformity conclusion are as follows: {a detailed justification should be provided}.>

1. Benefit risk assessment

[Update this section at Day 150/180/195. See Day 80 template/guidance for instructions; delete comment boxes from final report]

Section ‘5. Benefit risk assessment’ not applicable for biosimilar. Please replace by this section by the section called ‘biosimilarity assessment’ (see further below)

* 1. Therapeutic Context
		1. Disease or condition
		2. Available therapies and unmet medical need
		3. Main clinical studies
	2. Favourable effects

| **Comments** |
| --- |
| * Avoid interpretation and value judgements (e.g., it was convincingly shown that overall survival was greatly improved for treatment X).
* This section should be consistent with the favourable effects described in 5.6. Effects Table and with the [SmPC section 5.1](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf#page=20). No new results should be introduced here that have not been described in detail in the previous sections
* This section does not need to be updated during the procedure unless new key results are submitted

For more guidance on definitions of favourable effects, how to select “key” effects, and examples, see the *D80 assessment report Overview template/guidance+D120 LOQ*. |

* 1. Uncertainties and limitations about favourable effects
	2. Unfavourable effects

| **Comments** |
| --- |
| * Avoid interpretation and value judgements (e.g., low-grade toxicity for treatment X was significant);
* Try to avoid long lists of individual side-effects. If meaningful, try to group them (e.g., in terms of their consequences such as life-threatening reactions or by System Organ Classes).
* This section should be consistent with the unfavourable effects described in 5.6. Effects Table, the important identified risks described in section 3.4 Risk Management Plan, and the [SmPC Section 4.8](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf#page=15). No new results should be introduced here that have not been described in detail in the previous sections (typically under Clinical Aspects).
* This section does not need to be updated during the procedure unless new key results are submitted

For more guidance on how to describe unfavourable effects, see the *D80 assessment report - Overview & D120 LOQ template with guidance* . |

* 1. Uncertainties and limitations about unfavourable effects
	2. Effects Table

Table X. Effects Table for [insert product name and indication] <(data cut-off: …)>.

| **Effect** | **Short****Description** | **Unit** | **Treatment** | **Control** | **Uncertainties/****Strength of evidence** | **References** |
| --- | --- | --- | --- | --- | --- | --- |
| **Favourable Effects** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Unfavourable Effects** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Abbreviations:

Notes:

| **Comments** |
| --- |
| * The Effects Table is entirely based on the assessment of the key favourable and unfavourable effects, strength of evidence, limitations and uncertainties described in the previous sections. As such, there is no new element in the table that has not been described elsewhere.
* Ensure consistency between the table and the favourable, unfavourable effects and strength of evidence, uncertainties and limitations described above.
* The Effects Table should not replace the textual description of effects in the respective sections (some degree of redundancy is expected) although some numerical details can appear in the table only.
* Initially, the Effects Table should appear only in the CHMP/CAT Rapporteur’s Day 80 report. Subsequently, it should be merged at Day 120 List of Questions and kept updated throughout the assessment until the CHMP/CAT Day 210 report. The Effects Table is not needed for biosimilars.

For more details and examples on the Effects Table, see the *D80 assessment report - Overview & D120 LOQ template with guidance* . |

* 1. Benefit-risk assessment and discussion
		1. Importance of favourable and unfavourable effects

| **Comments** |
| --- |
| * Whereas previous sections mainly focus on description of the data, this section focuses on interpretation of the data, typically using value judgments about the importance of the observed effects and associated uncertainties and limitations of the data.
* In this section quantitative data and study descriptions do not need to be repeated. Instead, use value judgement to interpret the importance of the effects and the impact of any associated uncertainties and limitations of the data described in earlier sections.
* This assessment will require subjective judgements; expert and patient input (e.g., from literature or expert meetings, Scientific Advisory Groups) as well as relevant previous decisions should be taken into account and explained, if available.

For more details and examples, see the *D80 assessment report - Overview & D120 LOQ template with guidance .* |

* + 1. Balance of benefits and risks

| **Comments** |
| --- |
| * This section can be relatively short unless the impact of remaining uncertainties that have impact on the confidence in the benefit-risk balance and any limitations needs to be described in detail. Wordings like “the benefit/risk balance is **currently** **negative**” or “the benefit/risk balance is **currently** **undetermined**” may be the most adequate choice during the first phases of the assessment procedure.
* Consider explaining the reason for the proposed indication (restriction or generalisation compared to trial data; major deviations from previous wordings of the indications within the same therapeutic area). The place in therapy and duration of treatment may also warrant further discussion.

For detailed guidance on how to express tradeoffs and examples, see the *D80 assessment report - Overview & D120 LOQ template with guidance .* |

* + 1. Additional considerations on the benefit-risk balance

| **Comments** |
| --- |
| * Do not repeat previous sections. In particular, do not use this section to re-state important benefits, risks, uncertainties, their impact on the decision; these should have been described in previous sections.
* Consider discussing the consistency of this benefit-risk assessment with similar past assessments, and explain any differences.
* Is the benefit-risk balance expected to be the same over the time of treatment?
 |

<Conditional marketing authorisation>

*{Discuss the elements of comprehensive data that are not available}*

As comprehensive data on the product are not available, a conditional marketing authorisation <was requested by the applicant in the initial submission> <is proposed subject to consultation with the applicant>.

*In case a conditional marketing authorisation is supported [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.*

The product is considered to fulfil 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}*
* 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}* *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) disease not being considered life-threatening or seriously debilitating, (b) comprehensive data unlikely to be generated post-authorisation, (c) not addressing unmet medical need and (d) benefits of immediate availability not outweigh the risks, include here corresponding discussion.*

<Marketing authorisation under exceptional circumstances>

<As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances <was requested by the applicant in the initial submission> <is proposed , subject to consultation with the applicant>.>

*In case a marketing authorisation under exceptional circumstances is recommended [select text as applicable, at least one of the options must apply, and align section 1]:*

It is considered that the applicant has sufficiently demonstrated 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.

*In case a marketing authorisation under exceptional circumstances is not recommended.*

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 the 8. ‘Recommendations’ section><is negative>.

1. <Biosimilarity assessment>
	1. Comparability exercise and indications claimed
	2. Results supporting biosimilarity
	3. Uncertainties and limitations about biosimilarity
	4. Discussion on biosimilarity
	5. Extrapolation of safety and efficacy
	6. Additional considerations
	7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, <name of product> is considered <not> biosimilar to <reference product>. Therefore, a benefit/risk balance comparable to the reference product <can><cannot> be concluded.

1. List of outstanding issues to be addressed in an oral explanation and/or in writing
	1. Quality aspects

[Note: In case the ASMF procedure is used the following should be stated in case Major Objections or other concerns are being raised on the restricted part of the ASMF:]

“For <Major Objections> <and> <Other concerns> on the restricted part of the ASMF see separate LoOI on the ASMF”

* 1. Non clinical aspects
	2. Clinical aspects
	3. Risk management plan

• Safety specification

• Pharmacovigilance plan

• Risk minimisation measures

• Public summary of the RMP

The Applicant should update the Part VI “Summary of activities in the risk management plan by medicinal product”, in line with the issues raised in other parts of the RMP.

* 1. Pharmacovigilance
	2. <Orphan similarity and derogations>
	3. <New active substance status>
	4. <Additional data exclusivity /Marketing protection>
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 the risk management plan.

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

* 1. Proposed list of post-authorisation measures\*

[Please also consider Appendix 1 of the CHMP D150 JAR Clinical AR to fill in the below table. This table should be reserved to include post-authorisation measures that are part of the marketing authorisation, such as specific obligations, Annex II conditions, additional pharmacovigilance activities (category 3 studies in the RMP).]

| **Post-authorisation measure(s)** | **Motivation** |
| --- | --- |
| Proposed post-authorisation measure 1 with proposed classification: | Motivation/Background information on measure, including due date: |
| 1. |  |
| Proposed post-authorisation measure 2 with proposed classification: | Motivation/Background information on measure, including due date: |
| 2. |  |
| Proposed post-authorisation measure 3 with proposed classification: | Motivation/Background information on measure, including due date: |
| 3. |  |
| Proposed post-authorisation measure X with proposed classification: | Motivation/Background information on measure, including due date: |
| X. |  |

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

Proposed list of recommendations:

Recommendations pertain to quality, non-clinical (e.g. ERA, PK/PD, PAES if not key to the B/R).

| **Description of post-authorisation measure(s)** |
| --- |
|  |
|  |

* 1. Other conditions

[Please state in this section all additional risk minimisation measures.]

* 1. Summary of product characteristics (SmPC)

See attached (edited) product information.

* 1. Additional monitoring

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)>.

* 1. Labelling
	2. Package leaflet (PL)

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)). >

1. Appendices (as appropriate)
	1. <Rapporteurs><CHMP><CAT> questions on the ASM (active substance manufacturer) restricted part of the DMF

[NOTE that this annex should not be sent to the MAH but only to the holder of the DMF.]

* 1. AR on New Active Substance Claim dated < >
	2. AR on similarity dated < >
	3. AR on derogations dated < >
	4. AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies – Article 14(11) dated < >
	5. AR on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication – Article 10(5) dated < >
	6. AR on the significant non-clinical or clinical data in relation to the claimed new indication – Article 74a dated < >
1. QRD checklist for the review of user testing results

[for guidance please see D80AR Overview guidance]

**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/CoRapporteur |  |

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

- Focus test report provided [ ]  yes [ ] no

- Bridging form provided[[1]](#footnote-3) [ ]  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:

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

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

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

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

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

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

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

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

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

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

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

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

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

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. [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-3)