<Co>Rapporteur Day <60\*><80> critical assessment report

\*in case of accelerated assessment

Non-clinical aspects

<Product name>

International non-proprietary name: <INN> or <Common name\*\*>

\*\*e.g. for vaccines and some ATMPs

<Pharmaceutical form and strength>

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

Applicant:

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

Instructions to Applicants/Rapporteurs for use of this template

In the event that the **Applicant** agrees to pre-fill the factual sections of the template, guidance text for them is provided in blue.

The Applicant is expected to pre-fill the factual sections of this template in an objective data-driven way, without any bias or promotional intent.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. non-clinical overview, summary, study reports), references to the literature or other sources.

The use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate. PK/TK tables should include the number of animals and standard deviation for each parameter. For repeat-dose studies, TK day of sampling should be mentioned. Tables taken from the dossier may also be included into the assessment. Footnotes should not be forgotten. **Tables should be added as MS Word tables and not copy/pasted as pictures or from PDF.**

Separate pages have been added in the template to include a list of abbreviations and references, to be completed when necessary.

It is recommended that the font used in the main text be Verdana, size 9.

Moreover, in general, the following aspect should be considered when filling in the template:

* For each main section of the assessment report for module 4, the report should describe the data submitted in accordance with Annex I of Directive 2001/83/EC. The types of studies addressed within each section should include all indents as listed in Annex I of Directive 2001/83/EC section 4.2.
* Justifications should be provided for waiving certain studies or for substituting them with publications.
* If data from publications is used a clear referencing should be included allowing for clear identification of the publications. Consider generation of a reference list if a substantial number of publications is used.
* If some aspects of development are to be included, please introduce the non-clinical development programme factually in view of the proposed indication and posology (indicate if there is a paediatric indication or development). State if the range of studies is in agreement with relevant EU/ICH guidelines.

Prior to the submission of the completed template via Eudralink, the Applicant is asked to **remove any Protected Personal Data in the metadata of the document, such as name of author etc**. The applicant is also asked remove the blue guidance text only (not the green). See instructions below.

The principle of the template is to make clear distinctions between presentation of data (methodology and results) and the judgement (“Rapporteur’s comments”).

Guidance text for **(Co)Rapporteurs** is provided in green. If the Applicant has not agreed to pre-fill the factual sections, this will be done by the Rapporteur, and they can use the blue text as reference.

Because the Applicant is asked to complete only the factual sections of this report, it is expected that there should not be many cases of disagreements. However, Rapporteurs can choose to:

* Either amend the sections completed by the Applicant if they consider that the data has not been reported accurately.
* Or leave the applicant’s section as-is and comment on disagreements in the commenting boxes.

Specific assessment conclusions should in any case be included in the boxed sections of the report, not in the factual sections.

In general the following aspects should be considered:

* The data submitted should be assessed based on the legal basis of the application, other legal/regulatory data requirements, applicable guidelines and other scientific criteria.
* The report should be sufficiently detailed to allow for secondary assessment by other CHMP/CAT experts.
* The report should assess salient findings and especially those deficiencies that justify the questions for the Applicant. These questions will also be listed in the “CHMP AR/overview”.
* The report should indicate whether findings have implications for human safety and whether additional expertise is needed to assess this (e.g. there are findings regarding carcinogenicity but carcinogenic mechanisms are different between target species and man).
* The report should also emphasise findings that need to be reflected in the SmPC.
* For each type of study, the report should distinguish between main (pivotal) and supportive data.
* The report should indicate if acceptable justifications have been provided for waiving the need to conduct certain studies, replacing original studies by literature data or when data submitted deviate from the legislation and guideline requirements. If certain studies are only available as publications, it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in-depth assessment of crucial data.
* If data from publications is used in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generating a reference list if a substantial number of publications is used. If appropriate ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).

The list of non-clinical questions is to be included only in the CHMP AR/overview document. For reference please consider the following for the classification of the questions raised:

* “Major objections (MO)”, preclude a recommendation for marketing authorisation (e.g. GLP deviations, impurities toxicological characterisation, topics not superseded by clinical data (reprotox, genotox...). In principle, the major objection should start with a statement concerning the pivotal shortcoming, may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents. Ideally, the objection should include a clarification as to what kind of response/action is expected from the Applicant.
* “Other concerns (OC)”, may affect the proposed conditions for marketing authorisation and product information. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

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.

How to remove the guidance text:

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Guidance text – Applicant” or “Guidance text – Rapps” and “Guidance text – black” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

Administrative information

To be completed by the Applicant

|  |  |
| --- | --- |
| Product data |  |
| Product name |  |
| INN or Common Name |  |
| EMA Product Number |  |
| ATC code |  |
| Pharmaceutical form(s) and strength(s) |  |
| Route of administration(s) |  |
| Proposed indication |  |
| Orphan designation | <Yes/No> (if yes, include ODD number) |
| PRIME scheme | <Yes/No> |

To be completed by the assessment team:

|  |
| --- |
| Declarations  The assessment team should tick one or other of the 2 boxes below:  The (co)Rapporteur and/or the assessor confirm(s) that this assessment **does not** include non‑public proprietary information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments, development plans etc), irrespective from which entity was received.  The (co)Rapporteur and/or the assessor confirm(s) that this report **does** include non-public information (as described above), but all relevant paragraphs containing confidential information have been **highlighted in blue**, so that they can be removed before sharing the document with the Applicant or other parties. |

Table of contents

[List of abbreviations 7](#_Toc147753813)

[1. Introduction 8](#_Toc147753814)

[1.1 Type of application 8](#_Toc147753815)

[1.2 Therapeutic context 9](#_Toc147753816)

[1.3 Aspects of development 10](#_Toc147753817)

[1.4 Description of the product 10](#_Toc147753818)

[1.5 GLP aspects 11](#_Toc147753819)

[2. Pharmacology 12](#_Toc147753820)

[2.1 Primary pharmacodynamics 12](#_Toc147753821)

[2.2 Secondary pharmacodynamics 14](#_Toc147753822)

[2.3 Safety pharmacology 14](#_Toc147753823)

[2.4 Pharmacodynamic drug interactions 15](#_Toc147753824)

[2.5 (Co)-Rapporteur’s overall conclusions on pharmacology 16](#_Toc147753825)

[3. Pharmacokinetics 17](#_Toc147753826)

[3.1 Analytical methods 17](#_Toc147753827)

[3.2 Absorption 17](#_Toc147753828)

[3.3 Distribution 18](#_Toc147753829)

[3.4 Metabolism 19](#_Toc147753830)

[3.5 Excretion 21](#_Toc147753831)

[3.6 Pharmacokinetic drug interactions 21](#_Toc147753832)

[3.7 Other pharmacokinetic studies 22](#_Toc147753833)

[3.8 (Co)-Rapporteur’s overall conclusions on pharmacokinetics 23](#_Toc147753834)

[4. Toxicology 24](#_Toc147753835)

[4.1 <Single dose toxicity> 24](#_Toc147753836)

[4.2 Repeat-dose toxicity 25](#_Toc147753837)

[4.3 Genotoxicity 27](#_Toc147753838)

[4.4 Carcinogenicity 29](#_Toc147753839)

[4.5 Developmental and reproductive toxicology (DART) 31](#_Toc147753840)

[4.6 Toxicokinetics 37](#_Toc147753841)

[4.7 Interspecies comparison and exposure margins to clinical exposure 38](#_Toc147753842)

[4.8 Local tolerance 39](#_Toc147753843)

[4.9 Other toxicity studies 39](#_Toc147753844)

[4.10 Ecotoxicity/environmental risk assessment (ERA) 44](#_Toc147753845)

[4.11 (Co)-Rapporteur’s overall conclusions on toxicology 47](#_Toc147753846)

[5. Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP) 50](#_Toc147753847)

[6. List of references 51](#_Toc147753848)

List of abbreviations

To be completed by the Applicant (if they agreed to pre-fill the template).

Rapporteurs to add to applicant’s list if needed, or to complete fully if the applicant has not agreed to pre-fill the template.

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

1. Introduction
   1. Type of application

Indicate the type of marketing authorisation application (reference to the legal basis of the application); complete/abridged; whether for conditional approval or under exceptional circumstances. Also indicate whether accelerated assessment was applied for and granted or not granted.

|  |  |
| --- | --- |
| Eligibility to the Centralised Procedure | Only choose 1 and delete the rest  <Article 3(1) and point <1> <3> <4> of Annex of Regulation (EC) No 726/2004.>  <Article 3 (2) <(a)> <(b)> of Regulation (EC) No 726/2004.>  <Article 28 of Regulation (EC) No 1901/2006.>  <Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006.>  <Article 58 of (EC) No Regulation 726/2004 for a scientific opinion in the context of cooperation with the World Health Organisation.> |
| Legal basis | Only choose 1 and delete the rest  <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 fixed combination products.>  <Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product. >  <Article 10(1)> of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.>  <Article 10(3)> of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.>  <Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.>  <Article 58 of Regulation (EC) No 726/2004, - complete and independent application, by analogy to Article 8(3) of Directive 2001/83/EC.> |
| New Active Substance status claim | The Applicant indicates that <INN/common name> is considered to be a <new><known> active substance.> |
| Conditional marketing authorisation or authorisation under exceptional circumstances | <Not applicable> <The Applicant is applying for a <conditional marketing authorisation><marketing authorisation under exceptional circumstances>.> |
| Accelerated assessment | <Not applicable> <The Applicant submitted a request for accelerated assessment for <product name> on <date>. The application was <approved> <rejected> by CHMP at its meeting on <date>.> |

* 1. Therapeutic context

This section should be 1-3 pages in total length. A thorough summary of the literature is not expected in this document. In some cases (e.g., for less-well known or rare diseases), more information may be useful to help establish the therapeutic context relevant to the product under review. References for more detailed information can be provided.

Provide background on the medical condition that is necessary to understand the therapeutic context of this application or is otherwise relevant to the review. This section can be abbreviated if the condition is well-recognized. A good background typically includes the following:

* Disease definition and important clinical characteristics
* Natural history of the condition, in particular whether it generally progresses or remits and relapses, and whether there are subtypes with different patterns
* Major signs and symptoms, including their frequency, severity, and how they vary with disease severity, stage, or duration of illness
* Population affected (e.g., demographic groups, geographic and cultural considerations)
* Diagnostic criteria and methods used in clinical practice
* Incidence and prevalence of the condition, including rates of diagnosis, severity, mortality, and morbidity. Note any important variations across patient demographics or subpopulations.
* The impact the condition has on patients’ daily living (e.g., specific limitations, health-related quality of life issues), across the spectrum of severity. Consider the patients’ perspective about the impact of the condition, when known.
* Societal or global public health implications of the condition, if relevant (e.g., control and prevention, loss of productivity, etc.)
* Areas of uncertainty or limitations in understanding of the condition or its impacts.

Provide a succinct overview of therapies currently used in the EU to treat or prevent the condition in the claimed indication. It should indicate how well these treatment options meet the medical needs of the patient population and how the treatment armamentarium could be enhanced in terms of the benefit, safety, and tolerability of treatments.

If relevant, briefly describe other treatments used for the indication, such as drugs used off-label (only if supported by strong evidence), non-prescription drugs, medical and surgical procedures, and non-drug therapies such as diet modifications and physical therapy.

<Text>

* 1. Aspects of development

Briefly summarise the non-clinical development programme in view of the (proposed) indication and posologies. This section should be brief, with all the detail expected later on in this document.

Include if scientific advice was given, provide brief summary of it and indicate whether it has been broadly followed or not. Indicate if and when PRIME eligibility was granted.

Indicate whether a Paediatric Investigation Plan (with or without deferral) or a product-specific waiver has been agreed with the PDCO, or whether a class waiver applies. Briefly summarise the conditions and principal requirements of the paediatric investigation plan with regards to non-clinical aspects, if applicable, and state the relevant key information about the current status of the non-clinical studies (i.e. completed, studies ongoing, etc).

Indicate availability of non-clinical development impacting on other special populations such as in elderly, in males/females, etc.

**For biosimilars** the relevant guidelines have to be taken into consideration. Relevant product class specific guidelines are also available on the EMA website.

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU has to be provided. Highlight any differences in strength, pharmaceutical form, or formulation of the intended biosimilar relative to the reference product.

The detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical) needs to be provided in tabular format.

<Text>

* 1. Description of the product

Briefly describe the product being submitted. Mention the mechanism of action and whether it is already approved for use in any market. State the proposed indication and posology.

This section should be extremely brief and consist for the most part of the proposed SmPC sections 4.1 and 4.2.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  (Co)-Rapporteurs: if you consider the summary provided by the applicant to be factually incorrect (or that key information was omitted), please make a comment and describe the disagreement in this box.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. GLP aspects

**To be completed by assessors.**

In this section specifically address:

* Any concerns raised during the assessment about compliance with GLP requirements (data accuracy or protocol compliance). A useful tool to be used to identify the need for a triggered GLP inspection is the checklist “Triggers for audits of good laboratory practice (GLP)” http://www.ema.europa.eu/docs/en\_GB/document\_library/Regulatory\_and\_procedural\_guideline/2015/12/WC500199238.pdf
* Check the eCTD “Non-clinical studies GLP compliance (annex to the cover letter)”
* Discuss the need for a GLP inspection, particular in case of test facilities located in non-Mutual Recognition Agreement (MAD) countries (please, refer to M1, annex to cover letter).

To request a GLP inspection:

* Contact your national GLP monitoring authority.
* Contact EMA inspection office - GLP inspection coordination.
* Determine with them the studies, sites and special concerns or issues related to the inspection.
* EMA inspection office formulates the formal inspection request for review by the inspectors and agreement by the Rapporteur and Co-Rapporteur prior to adoption by CHMP (day 90 or 120).

<Text>

1. Pharmacology
   1. Primary pharmacodynamics

Please complete this section and its subsections with factual data based on eCTD section 2.6.2.2 and relevant instructions as per notice to Applicants and relevant guidelines (ICH and others).

This section should address PD studies in relation to the disease to be treated and the proposed indications including factual data on relevant points e.g. (but not only limited to): proof of concept (in-vitro and in-vivo), mode of action, relevant animal models, interspecies comparison, activity (e.g. ED50) including the species used in toxicology studies, preliminary PK (plasma concentration) in animal models (PK/PD relationship), duration/reversibility of effects, pharmacologically active metabolites and chiral implications((relative contribution to pharmacodynamics). Consider as well specificity of pharmacodynamics for anti-infectives (e.g. spectrum of activities, mechanism of resistance, etc) and prophylactic vaccines (immunogenicity i.e., the ability to induce a humoral and/or cell-mediated immune response).

For biosimilars:

A battery of receptor-binding studies or cell-based assays, (many of which may already be available from quality-related assays), are normally a part of the comparability exercise in order to assess if any differences in reactivity are present and to determine the likely causative factor.

Include factual information on the adequacy (state of the art) of the in-vitro assays used, with particular attention to sensitivity, specificity and ability to provide evidence that observed differences in performance in in-vitro assays are clinically not relevant. Provide factual information on the concentration range used and the number of batches of the reference product and of the biosimilar representative of the material intended for clinical/commercial use.

The functionality of in-vitro assays should cover all the relevant modes of action claimed in the indications.

If in-vivo animal studies have been performed, provide details of the relevance of the in-vivo model in order to provide complementary information on biosimilarity in addition to the totality of data obtained (including quality, in-vitro and clinical data).

* + 1. In-vitro

Please refer to the guidance text above.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology/mechanism of action.  Comment also whether in-vitro data support that the selected test species (for safety studies) are pharmacologically relevant (e.g. whether the potency of the product is similar).  For biosimilars:  Discuss the adequacy (state of the art) of the in-vitro assays used, with particular attention to sensitivity, specificity and ability to provide evidence that observed differences in performance in in-vitro assays are clinically not relevant. Discuss the concentration range used and the number of batches of the reference product and of the biosimilar representative of the material intended for clinical/commercial use.  The functionality in-vitro assays should cover all the relevant modes of action claimed in the indications.  If in-vivo animal studies have been performed, discuss the relevance of the in-vivo model in order to provide complementary information on biosimilarity in addition to the totality of data obtained (including quality, in-vitro and clinical data).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. In-vivo

Please refer to the guidance text above.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Secondary pharmacodynamics

Please complete with factual data based on eCTD section 2.6.2.3 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

This section should provide factual data on pharmacological effects (off-target, on-target/off-tissue) other than the primary therapeutic activity (previously general pharmacology). Studies/data on secondary pharmacodynamics should be summarised by organ system, where appropriate, and evaluated in this section.

<Text>

|  |
| --- |
| (Co)-Rapporteur s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Safety pharmacology

Please complete with factual data based on eCTD section 2.6.2.4 and relevant instructions as per notice to Applicants and relevant guidelines (ICH and/or relevant others). Avoid repetition of the same data in text and tables.

GLP status should be mentioned.

<Text>

Table 1: Summary of safety pharmacology studies

Please complete for relevant studies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID/ GLP | Study type | Test system | Concentration/ dose/ route | Major results |
| <Text> | <Text> | <Text> | <Text> | For assessors to complete  <text> |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Reminder: Safety pharmacology studies are not required for biosimilars or for locally acting products with negligible systemic exposure. Safety pharmacology endpoints may be also evaluated as part of the general toxicity studies. In this case safety pharmacology aspects/results should be presented here and a cross reference between section 2.3 and section 4 should be included  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology. Special attention should be given to the time points selected for the endpoint measurements that should be based on PD and (clinical) PK considerations (e.g. Cmax).  Comment if some safety pharmacology endpoints are incorporated in the design of toxicology, kinetic, clinical studies, etc.  The following should be commented in this section:  - Cardiovascular system (in-vitro (e.g. hERG assay) and in-vivo)  - Central nervous system  - Respiratory system  - Other relevant (e.g. renal or gastrointestinal)  For biosimilars:  Safety pharmacology studies are not required for similar biological medicinal products.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Pharmacodynamic drug interactions

Please complete with factual data based on eCTD section 2.6.2.5 and relevant instructions as per notice to Applicants and relevant ICH guidelines. A table summarizing the in-vitro studies performed (inhibition of CYPs, transporter…), their results (IC50/Ki) and the predicted concentration of drugs and metabolites at the site of interaction (plasma, intestine, liver and kidneys) could be considered.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology. In particular, interactions at receptor level and possible co-medications in the clinical setting, should be considered.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. (Co)-Rapporteur’s overall conclusions on pharmacology
     1. Discussion:

The contents of this section should be written so that they can be copied/pasted directly to the CHMP AR/Overview.

Briefly summarise the high-level results of the main studies, emphasising their ability to predict activity and potential adverse events in humans.

Highlight areas of disagreement with module 2.4 and any issues requiring clarification. Include comments on the suitability of the proposed SmPC text. Ensure correspondence with SmPC section 5.1 “mechanism of action” and “pharmacodynamic effects”, if relevant.

<Text>

* + 1. Conclusion:

A very brief summary of the conclusions drawn from the pharmacology should be provided here.

<Text>

1. Pharmacokinetics
   1. Analytical methods

Please complete with factual data based on eCTD section 2.6.4.2 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

For immunogenicity assays(e.g. for prophylactic vaccines or biological products) also address drug tolerance of the assay and whether any subjects are classified with inconclusive Anti Drug Antibody (ADA)status.

As a general rule please provide tabulated data as much as possible including essential information regarding methods (e.g. validation or qualification, sensitivity of tests, etc). Units of measurement should be clearly defined (e.g. molarity or mg/ml) and the same units used consistently as much as possible.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Comment if the analytical methods have been submitted and made available and describe if they are adequate and whether they have been sufficiently validated. GLP compliance should be considered when relevant.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Absorption

Please complete with factual data based on eCTD section 2.6.4.3 and relevant instructions as per notice to Applicants and relevant ICH guidelines. This section should be very brief, unless justified. Applicants can limit their entry to the table below if preferred.

If appropriate, include single and repeat-dose studies as well as absolute and relative bioavailability.

Clarify whether PK parameters refer to unbound/free fraction or total; this is particularly relevant for e.g., pegylated forms.

GLP status should be mentioned.

<Text>

Table 2: absorption data:

Please complete for relevant studies.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Day | Dose (mg/kg)/ route | N/Sex | T1/2  (hr) | Tmax (hr) | Cmax (ng/mL) | AUC0-Tlast (hr•ng/mL) | AUCINF  (hr•ng/mL) |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |

|  |
| --- |
| (Co)-Rapporteur’s comments:  The following aspects should be considered: dose proportionality, gender difference.  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Distribution

Please complete with factual data based on eCTD section 2.6.4.4 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

Discuss the degree of distribution in relation to the possible target organs for toxicity and tissue retention if applicable.

Shedding through animal secretions and/or excreta for anti-infectives and viral vector-based products, should be provided.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  The following data should be considered:   * Tissue distribution studies and mention of method (e.g. quantitative whole body autoradiography) * Protein binding (albumin, other) in different species with estimation of the free fraction including humans. * Distribution in blood cells if possible (not systematically done). * Distribution across Blood Brain Barrier. * Placental transfer studies. * Excretion in the milk should be highlighted.   Discuss degree of distribution in relation to possible target organs for toxicity and tissue retention if applicable (especially if effects at site of retention).  Plasma protein binding should be considered. Data in humans and inter-species comparisons should be commented upon. If there are indications of melanin binding, the need for assessment of phototoxicity should be discussed.  Distribution of parent compounds vs metabolites to be discussed in this context as appropriate.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Metabolism

Please complete with factual data based on eCTD section 2.6.4.5 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

The following data should be considered under the following headings:

* Chemical structures and quantities of metabolites in biological matrices (table).
* Possible metabolic pathways (add picture if available).
* Presystemic metabolism (gastro intestinal/hepatic first-pass effects).
* In-vitro metabolism, mainly cytochrome P450 (microsomal) studies: affinity, substrate specificity for subfamilies, inhibition studies (if positive, type of inhibition: reversible, permanent, irreversible, competitive), drug interactions (clinically relevant associations). Non-microsomal oxidations, reduction, hydrolysis if applicable.
* Enzyme induction.
* Phase II (conjugation) metabolism mainly in-vivo.

It is important to compare metabolic patterns in animals and humans. Identify if there are species-specific metabolites, particularly if the animals used for safety testing do not form metabolites that have been identified in humans.

Please note that relevant in-vitro metabolism data (e.g. CYP inductions/inhibitions on human microsomes, effect on transporters, etc.) should be presented here with a clear focus on non-clinical aspects. If applicable a cross reference to the clinical report may be made.

Include a description of the possible metabolic pathways; discuss presystemic metabolism as well as in-vitro metabolism and enzyme induction.

Indicate the possibility of inter-conversion in-vivo. Lack of stereoselective metabolism in the chiral centre in nonclinical species and/or man or the absence of clinical consequences of inter-conversion should be justified.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  It is important to compare metabolic patterns in animals and humans. Identify if there are species-specific metabolites. Discuss the relevance of the animal data/model provided.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Excretion

Please complete with factual data based on eCTD section 2.6.4.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

Please provide data on routes of excretion which could be of value for the assessment of organ-specific toxicity, excretion unchanged, clearance, as well as information on any potential accumulation. Data on mass balance should be included.

<Text>

Table 3: Excretion data:

Please complete for relevant studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | N | Dose  (mg/kg)/ route | Urine  (% dose) | Faeces (% dose) | Bile (% dose) | Carcass (% dose) | Cage wash (% dose) | Recovery  (% dose) | Time  (h) |
|  |  |  | ± | ± | ± |  |  | ± | ± |
|  |  |  | ± | ± | ± |  |  | ± | ± |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Pharmacokinetic drug interactions

Please complete with factual data based on eCTD section 2.6.4.7 and relevant instructions as per notice to Applicants and relevant ICH guidelines. Please note that in-vitro experiments addressing interaction risks (e.g. inhibition or induction of CYP-enzymes or transporter proteins) could also be presented in the clinical AR section 2.2.9. To avoid duplication of data a cross-reference to the clinical AR is appropriate here.

Focus on interactions with drugs that are potentially going to be co-administered in the clinical situation.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology and further instructions suggested in the product information.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Other pharmacokinetic studies

Please complete with factual data based on eCTD section 2.6.4.8 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

If relevant, include information regarding studies in juvenile animals, in pregnant animals or in animal models of disease.

This section should report data on Pharmacokinetics study that cannot be included in the section above.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. (Co)-Rapporteur’s overall conclusions on pharmacokinetics
     1. Discussion:

The contents of this section should be written so that they can be copied/pasted directly to the CHMP AR/Overview.

Briefly summarise the high-level results of the main studies, emphasising their ability to predict potential adverse events in humans. Give an overview of the salient pharmacokinetic features. Comment on the relevance of the animal species used in the toxicity testing for human safety assessment e.g. considering metabolic patterns. Other important aspects may include major differences in absorption/bioavailability, interindividual/interspecies variability, elimination rates (differences in t½), etc. Discuss any PK/PD relationship.

Comment on other issues that may be of importance for the safety assessment e.g. distribution to target organs, excretion routes, and pharmacologically active metabolites/stereoisomers. Comment on any inter-species variability where relevant.

Ensure correspondence with SmPC (particularly section 5.3 Preclinical safety data but also e.g., sections 5.1 Mode of action, 5.2 Pharmacokinetic properties, 4.3 contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, if relevant) and that all information in the SmPC is explicitly assessed and supported by the scientific assessment. Include comments on the suitability of the proposed SmPC text.

Highlight areas of disagreement with module 2.4 and any issues requiring clarification. Discuss interspecies differences and compare with the clinical situation.

<Text>

* + 1. Conclusion:

A very brief summary of the conclusions drawn from the pharmacokinetics should be provided here.

<Text>

1. Toxicology

Comparison of active substance batches used in Toxicology and Safety Pharmacology (possibly mentioned also in section 2.3) studies with active substance batches used in clinical trials, should be provided.

* 1. <Single dose toxicity>

Please complete with factual data based on eCTD section 2.6.6.2 and relevant instructions as per notice to Applicants and relevant ICH guidelines if single dose toxicity studies were performed.

GLP status should be mentioned. Include the maximum tolerated dose or the observed maximum non-lethal dose as well as the clinical signs of acute toxicity (briefly), the mode and time of death (early/same day or delayed) and target organs, (histo)pathology if available. The duration of observation (14 days in a standard GLP study) and a short statement on whether studies revealed low or high acute toxicity should be included.

<Text>

Table 4: Single dose toxicity studies:

Please complete for relevant studies. The Column titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/day) | **Exposure** | | **Major (alt. Salient) findings**  <text>  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility (if data available). |
| Species  Duration + recovery (weeks)    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Single-dose toxicity studies (MTDs highlighted)** | | | | | |
| Example:  MOUSE (CD-1)  PO    GLP        (BS20210) | Main:  10M/10F    TK satellites:  5F/5M | 0 | - | - | ≥400 mg/kg …..    ≥600… |
| 100 | xx | xx |
| 400 | xx | xx |
| 600 | xx | xx |
|  |  |  |
| **Expansion on salient findings**  This row can be deleted if table is copied into the overview.    To be completed by assessors  Findings grouped by endpoint e.g.  Mortalities  Clinical signs  Clin chem  Hematology  Macroscopic findings  Microscopic findings | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it covers and supports the proposed indication/posology. Note: lack of single-dose studies may be acceptable if information on acute toxicity is available from other studies.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Repeat-dose toxicity

Please complete with factual data based on eCTD section 2.6.6.3 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

Please avoid lengthy text and rather focus on clear content for the table below. Relevant information should be mentioned:

* The pivotal studies should be organised by species and route of administration. Comment on GLP status for overall programme and specify any deviations (e.g. contamination of controls).
* A short description of the design (strain, route of administration, dose groups, number animals/gender/group, recovery groups if any, TK if performed).
* The main findings should be comprehensively described, namely death, body weight, relevant laboratory findings, target organs with type of histopathological lesions, dose-dependency, onset, severity, species or gender related differences and duration of toxic effect.
* The No Observed Adverse Effect Level (NOAEL) in the different species should be provided (if established) with comments on the relation of the systemic exposure at that dose level to the systemic exposure in humans given the maximum intended dose (exposure margin).
* A statement whether reversibility has been demonstrated in the recovery group should be included.
* Comments on TK (linearity, gender dependency, accumulation).
* Highlight the important findings; discuss the mechanistic background and the margin to the clinical exposure.

<Text>

Table 5: Repeat-dose toxicity studies:

Please complete for relevant studies. The Row titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/  day) | **Exposure** | | **Major findings & NOAEL**  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility. |
| Species  Duration + recovery (weeks)    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Repeat-dose toxicity studies (NOAELs highlighted)** | | | | | |
| Example:  MOUSE (CD-1)    12 + 4 w    PO    GLP        (BS20210) | Main:  10M/10F    Recovery:  5F/5M  TK satellites:  5F/5M | 0 | - | - | Example:  ≥200 mg/kg …..    ≥400 mg/kg.....      **NOAEL 100 mg/kg** |
| 100 | 524 | 1580 |
| 200 | 1203 | 3522 |
| 400 | 3010 | 8952 |
|  |  |  |
| **Expansion on salient findings**  This row can be deleted if table is copied into the overview.  To be completed by assessors  Findings grouped by endpoint e.g.  Mortalities  Clinical signs  Clin chem  Hematology  Macroscopic findings  Microscopic findings | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  The main findings can be included in the table itself and do not need to be repeated here. Reversibility of the event should be discussed as appropriate. Here you can highlight the importance of the findings, discuss the mechanistic background and the margins to clinical exposure.  For biosimilars: If an in-vivo safety study has been performed, discuss the relevance of the study in order to provide complementary information on biosimilarity in addition to the totality of data obtained (including quality, in-vitro and clinical data).  Studies regarding reproduction toxicology, mutagenicity and carcinogenicity are not required for similar biological medicinal products.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Genotoxicity

Please complete with factual data based on eCTD section 2.6.6.4 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

GLP status should be mentioned.

Please avoid lengthy text and rather focus on clear content for the table below. Relevant information should be included regarding:

* Overview of the tests performed.
* Sort the performed tests according to the ‘level’ of genotoxicity, i.e. mutagenicity (gene mutations), chromosomal aberrations (clastogenicity) in-vitro and in-vivo, primary DNA damage and other genotoxic effects.
* The relevance of the species used in the in-vivo tests as well as of the system used for metabolic activation (e.g. S9 fraction) in the in-vitro tests, based on comparisons with the metabolic pattern in humans should be commented on.
* A statement on the exposure should always be included for the in-vivo tests (refer to toxicokinetics studies).

If there are no remarkable findings in the in-vitro tests, inclusion in the table is sufficient.

<Text>

Table 6: Overview of genotoxicity studies

Please complete for relevant studies. The column titled “Results positive/negative/equivocal” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of test/study ID/GLP** | **Test system** | **Concentrations/**  **Concentration range/ Metabolising system** | **Results**  **positive/negative/equivocal** |
| Gene mutations in bacteria | Salmonella strains | +/- S9 | For assessors to complete  <text> |
| Gene mutations in mammalian cells | CHO-cells, HGPRT-locus | +/- S9 | For assessors to complete  <text> |
| Chromosomal aberrations in-vivo | Mouse, micronuclei in bone marrow | +/- S9 | For assessors to complete  <text> |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  If there are no remarkable findings, no need to go beyond the table above.  When evaluating genotoxicity tests please consider and comment on the following issues:  For in-vitro tests:   * Which strains /cells are used and which endpoints. * Selection of concentrations. * Stability in the medium (check of concentration/degradation products). * Metabolising system. * Positive and negative controls. * Treatment time/sampling time. * Applicant’s criteria for positive response. * Concentration-response relationship. * Reproducibility. * Cytotoxicity / cell survival.   For in-vivo tests:   * Which species/strain/model are used. * Number and gender of animals. * Selection of doses. * Exposure established by toxicity or kinetics. * Metabolic differences between species and human. * Treatment and sampling times. * Applicant’s criteria for positive response. * Dose/time-response relationship.   Issues to discuss:   * positive findings in either in-vitro or in-vivo tests * mechanistic background: mutagenic or clastogenic * is a threshold approach possible? (if yes, what is the margin of safety with human plasma level/exposure?) * conclusions on the genotoxic potential.   <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Carcinogenicity

Please complete with factual data based on eCTD section 2.6.6.5 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

Give a short presentation of the studies that have been performed, preferably as a table (see below). If carcinogenicity studies have not been performed, a justification should be provided. Give a short summary of results including neoplastic changes as well as relevant non-neoplastic changes, as appropriate. Non-neoplastic changes should be discussed with reference to the observations in repeat-dose toxicity studies. Preferably, list results in Table. If present, please provide with mechanistic studies to explain a tumorigenic effect of the product or metabolite(s).

GLP status should be mentioned.

<Text>

Table 7: Overview of carcinogenicity studies

Please complete for relevant studies. The column titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study details** | **No.Sex/ Group** | **Dose** (xg/kg/  day) | **Exposure** | **Major (alt. Salient) findings**  For assessors to complete  <text> |
| Species  Duration (weeks)    Route    GLP status    (Study ID) |  |  | AUC  xg/ml/h |
| **Carcinogenicity studies (NOAELs highlighted)** | | | | |
|  |  | 0 | - | ≥xx mg/kg …..    ≥xxx… |
| x |  |
| xx |  |
| xxx |  |
|  |  |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  If there are no remarkable findings, no need to go beyond the table above. Consider in the assessment:   * Species strain and gender. * Number of groups (control groups). * Number of animals per group. * Route of administration. * Duration of treatment. * Growth (body weight gain and food consumption). * Survival at the end of the study. * Toxicokinetics (in a table: day of sampling, AUC). Sampling of controls * Significance of tumour findings organs and tumour type (carcinoma, sarcoma, ....), and tumour incidence. * Pre-neoplastic findings. * Nomenclature of tumours. * Statistical methods used. * Toxic findings not seen in the studies of shorter duration.   In general, consider the weight of evidence including repeated-dose toxicity study results, mode of action, class effects, and literature data, to come to a conclusion on the carcinogenicity potential.  If present discuss mechanistic studies to explain a tumorigenic effect of the product or metabolite(s).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Developmental and reproductive toxicology (DART)

If needed please complete with a short factual introduction based on eCTD section 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines. When all aspects are covered by the subsections below, the introduction can be omitted.

<Text>

* + 1. Fertility and early embryonic development

Please complete with factual data based on eCTD section 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines. Give a summary presentation of the performed studies, preferably in a table (example below) including dose-finding studies, as appropriate.

GLP status should be mentioned.

<Text>

Table 9: Summary table

Please complete for relevant studies. The column titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/  day) | **exposure** | | **Major (alt salient) findings & NOAEL**  <Text>  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility |
| Species  treatment period    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Fertility and early embryonic development studies (NOAELs highlighted)** | | | | | |
| Example:  Rat (Crl-WI/Han)      Prior to mating until GD 6  PO    GLP        (BS20210) | 20F | 0 | - | - | ≥200 mg/kg …..    ≥400… |
| x |  |  |
| xx |  |  |
| xxx |  |  |
|  |  |  |
| **Expansion on salient findings**  This row can be deleted if table is copied into the overview.  To be completed by assessors  Findings grouped by maternal/fetal effects and endpoints | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  Consider information relevant to reproduction toxicity from other sections of the dossier, either as cross-reference or facts. For instance, histopathology of reproductive organs from repeat-dose toxicity, endocrine effects, pharmacokinetics, pharmacodynamics should be considered.  If no major findings, no need to go beyond the table above.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Embryo-fœtal development

Please complete with factual data based on eCTD section 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines. Also consider information relevant to reproduction/teratogenicity from other sections of the dossier, e.g. histopathology of reproductive studies from repeat-dose toxicity, endocrine effects, PK (distribution and tissue distribution) and PD.

GLP status should be mentioned.

<Text>

Table 10: Summary table

Please complete for relevant studies. The column titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/  day) | **exposure** | | **Major (alt salient) findings & NOAEL**  <text>  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility |
| Species  treatment period    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Embryo-fetal toxicity studies (NOAELs highlighted)** | | | | | |
| Example:  Rat (Crl-WI/Han)      GD 6-19  PO    GLP        (BS20210) | 20F | 0 | - | - | ≥200 mg/kg …..    ≥400… |
| x |  |  |
| xx |  |  |
| xxx |  |  |
|  |  |  |
| **Expansion on salient findings**  <text>  This row can be deleted if table is copied into the overview.  To be completed by assessors  Findings grouped by maternal/fetal effects and endpoints | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  If no major findings, no need to go beyond the table above.  Also consider maternal toxicity and information relevant to reproduction/teratogenicity from other sections of the dossier, e.g. histopathology of reproductive studies from repeat-dose toxicity, endocrine effects, PK (distribution and tissue distribution) and PD.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Prenatal and postnatal development, including maternal function

Please complete with factual data based on eCTD section 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

GLP status should be mentioned.

<Text>

Table 11: Summary table

Please complete for relevant studies. The column titled “Major findings” (shaded grey) should be left empty as it will be completed by the assessors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/  day) | **exposure** | | **Major (alt salient) findings & NOAEL**  <text>  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility |
| Species  treatment period    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Prenatal and postnatal development studies (NOAELs highlighted)** | | | | | |
| Example:  Rat (Crl-WI/Han)      GD 6-PND20  PO    GLP        (BS20210) | 20F | 0 | - | - | ≥200 mg/kg …..    ≥400… |
| x |  |  |
| xx |  |  |
| xxx |  |  |
|  |  |  |
| **Expansion on salient findings**  <text>  This row can be deleted if table is copied into the overview.  To be completed by assessors  Findings grouped by maternal/fetal effects and endpoints | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  Comment if enhanced pre- and postnatal development(ePPND) study (e.g., for the non-human primate), is justified.  Consider maternal toxicity.  Evaluate exposure and distribution data in pregnant and/or lactating animals, and in offspring (including milk excretion).  Also consider information relevant to reproduction/teratogenicity from other sections of the dossier, e.g. histopathology of reproductive studies from repeat-dose toxicity, endocrine effects, PK (distribution and tissue distribution) and PD.  Provide suggestions and justifications for SmPC recommendations for sections 4.3, 4.6, 5.3.  If no major findings, no need to go beyond the table above.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Please complete with factual data based on eCTD section 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

GLP status should be mentioned.

Provide factual data of the tested systems used (e.g. species/strain, based on comparative metabolism and kinetics, comparative pharmacodynamics, age of juvenile animals).

Provide factual data on exposure and distribution data in

pregnant and/or lactating animals, and in dosed offspring (including milk excretion).

Data can be summarized in the table below.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study details** | **No:Sex/ Group** | **Dose** (xg/kg/  day) | **exposure** | | **Major (alt salient) findings & NOAEL**  <text>  To be completed by assessors. This column should provide a summary of main findings. Also comment on reversibility/ irreversibility |
| Species  treatment period    Route    GLP status    (Study ID) |  |  | Cmax  xg/ml | AUC  xg/ml/h |
| **Juvenile animal toxicity studies (NOAELs highlighted)** | | | | | |
| Example:  Rat (Crl-WI/Han)      PND 6-63  PO    GLP        (BS20210) | 20F | 0 | - | - | ≥200 mg/kg …..    ≥400… |
| x |  |  |
| xx |  |  |
| xxx |  |  |
|  |  |  |
| **Expansion on salient findings**  <text>  This row can be deleted if table is copied into the overview.  To be completed by assessors  Findings grouped by maternal/fetal effects and endpoints | | | | | |
| xxxx | xx | x | x | x | xxx |
|  | | | | | |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  Juvenile animal studies are designed for safety evaluation of pharmaceuticals intended for development in paediatric populations: reference to the Paediatric Investigation Plan should be made.  Include critical assessment on each specific area of the studies and provide concluding remarks considering relevant findings.  Consider margins of exposure and assess the clinical relevance of the findings.  Provide suggestions and justifications for SmPC recommendations.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Toxicokinetics

Please summarise with factual TK data from all toxicity studies(repeat-dose toxicity, developmental and reproductive toxicology, in-vivo genotoxicity, carcinogenicity studies etc.) based on eCTD section 2.6.6.3, 2.6.6.4, 2.6.6.5 and 2.6.6.6 and relevant instructions as per notice to Applicants and relevant ICH guidelines, provided that a TK part is included.

Please complete for relevant toxicity studies indicating exposure at study initiation and termination. Clarify whether TK parameters refers to unbound/free fraction or total; this is particularly relevant for e.g. pegylated forms.

Interim exposure data may be also considered, if deemed useful.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID/ species** | **Dose**  **(/)** | **Study day** | **Animal AUC**  **(ng·h/ml)** | | **Cmax**  **(ng/ml)** | |
| ♂ | ♀ | ♂ | ♀ |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

|  |
| --- |
| (Co)-Rapporteur’s comments:  For biological products: assess the impact of ADA (neutralising or not-neutralising) on exposure (cross refer to section 4.9.1 antigenicity).  Assess if the Applicant had a reasonable justification for the margins of exposure.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Interspecies comparison and exposure margins to clinical exposure

Please determine safety exposure margins based on animal exposure (Cmax and/or AUC) at the respective NOAEL in toxicity studies compared to human levels.

Please complete for relevant toxicity studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID/ species** | **NOAEL**  **(/)** | **Animal AUC**  **(ng.h/ml)** | | **Cmax**  **(ng/ml)** | | **Animal:Human**  **XXX**  **Exposure Multiple** | |
|  |  | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
|  |  |  |  |  |  |  |  |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  The main findings can be included in the table itself and do not need to be repeated here. Here you can highlight the importance of the findings, discuss the mechanistic background and the margins to clinical exposure.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Local tolerance

Please complete with factual data based on eCTD section 2.6.6.7 and relevant instructions as per notice to Applicants and relevant ICH guidelines.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  Consider local irritancy at the site of administration/absorption (e.g. gastrointestinal for oral administration). Sensitisation studies (e.g., guinea pig assay) should be included if applicable (dermal route).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Other toxicity studies

Any such studies should be noted and findings factually reported.

* + 1. Antigenicity

Please include factual data on immune-related undesirable effects due to the ability to specifically combine with the final products of the immune response (secreted antibodies and/or surface receptors on T cells). If relevant, cross refer to section 4.6 toxicokinetics.

This is relevant for biological medicinal product (see ICH guideline).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  For biosimilars: the comparison of the ADA response to the biosimilar and the reference product in an animal model is not recommended as part of the biosimilar comparability exercise, due to the low predictivity for the immunogenicity potential in humans.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Immunotoxicity

Specific immunotoxicity (unintended immuno suppression or enhancement) investigations should be reported, especially when clinical implications are suspected. Such studies may include cell surface markers (immuno-histology or flow cytometry), functional tests (primary antibody formation to sheep red blood cells, NK activity, macrophagic function, delayed hypersensitivity, host resistance tests, complement activation…) etc. See relevant ICH guidelines.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  Discuss implications for immune suppression, autoimmune potential and hypersensitivity reactions in humans.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Dependence

Include factually any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in non-clinical experiments.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Studies on metabolites

Please provide factual data from module 2.6.6.8 on specific studies for major human metabolites (or isomers) insufficiently present in animals.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Studies on impurities

Please provide factual data from module 2.6.6.8 on studies for qualification of impurities: single or repeat dose, genotoxicity, reproduction. See ICH guidelines. Cross refer to quality module, as appropriate.

For mutagenic impurities (including nitrosamines and other cohort of concern impurities according to ICH M7 guideline), see also EMA guidance published on its website.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Phototoxicity studies

Please provide factual data from module 2.6.6.8 on studies on Phototoxicity if appropriate. Includes dermal/ocular photoxicity (when relevant), photosensitisation, etc.

The possible need for such studies depends on photo-absorption/degradation, dermal/ocular use/exposure (see relevant ICH and CHMP guidance).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Excipient studies

Please provide factual data from module 2.6.6.8 on studies on excipients if appropriate.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  Consider toxicological aspects of novel excipients.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Other (toxicity) studies (including mechanistic studies)

Please provide factual data from module 2.6.6.8 on any other toxicity study if appropriate.

If present, e.g. mechanistic studies to explain a tumorigenic effect or other toxic findings of the product or metabolite(s) (e.g. (mitochondrial toxicity, Hb reactivity etc.).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* 1. Ecotoxicity/environmental risk assessment (ERA)

Please complete a summary based on eCTD section 1.6.2. The ERA section of the AR should contain detailed factual assessment of the data submitted in accordance with the current guideline (EMEA/CHMP/SWP/4447/00) with a summary of the main study results (see table below). Please provide a conclusion on the potential risks to the environment and if necessary, recommendations for mitigation measures.

<Text>

If studies have been submitted, please fill out the part/table(s)below. Where data are not provided, not accepted nor required, the corresponding row should be deleted.

Table 11: Screening

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Substance (INN/Invented Name): | |  | | |
| CAS-number (if available): | |  | | |
| ***PBT screening*** |  | | Result | **Conclusion** |
| *Bioaccumulation potential-* log *K*ow | OECD107/117/123 | |  | Potential PBT: Y/N |
| ***PBT-assessment*** | | | | |
| **Parameter** | **Result relevant for conclusion** | |  | **Conclusion** |
| Bioaccumulation | log *K*ow | |  | B/not B |
| BCF | | L/kgww | B/vB/not B |
| Persistence | DT50  Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C  or ready biodegradability | | D | P/vP/not P |
| Toxicity | NOEC or CMR | |  | T/not T |
| **PBT-statement :** | <The active substance is considered to be not PBT, nor vPvB>  <The active substance is considered to be vPvB>  <The active substance is considered to be PBT>  <The active substance is considered to be PBT and vPvB> | | | |

Table 12: Phase I

|  |  |  |  |
| --- | --- | --- | --- |
| Phase I |  |  |  |
| Calculation | Value | Unit | Conclusion |
| PECsw,default/refined |  | µg/L | ≥ 0.01 threshold: Y/N |
| Other concerns (e.g. chemical class) |  |  | Y/N |

Table 13: Phase II – Physical-chemical properties and fate

|  |  |  |  |
| --- | --- | --- | --- |
| Phase II - Physical-chemical properties and fate | | | |
| Study type | Test protocol | Results | Remarks |
| Adsorption-Desorption  Soil 1 = type (e.g. sandy loam / clay / loamy sand)  Soil 2 = type  Soil 3 = type  Sludge 1 = Name  Sludge 2 = Name | OECD 106 or … | *K*oc, soil 1 = L/kgoc  *K*oc, soil 2 = L/kgoc  *K*oc, soil 3 = L/kgoc  *K*oc, sludge 1 = L/kgoc  *K*oc, sludge 2 = L/kgoc | List all values |
| Ready Biodegradability Test | OECD 301 |  |  |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems  Sediment 1 = type (e.g. sandy loam / clay / loamy sand)  Sediment 2 = type | OECD 308 | DT50, water = X / X d  DT50, sediment = X / X d  DT50, whole system = X / X d  shifting to sediment = X%  CO2 = X%  NER = X%  Transformation products >10% = Y/N,  TP1 = %,  DT50 M1: d | DT50s at X°C  1 / 2  at day X  at test end  at test end |

Table 14: Phase IIa effect studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Phase IIa effect studies | | | | | |
| Study type | Test protocol | Result | Value | Unit | Remarks |
| Algae, Growth Inhibition Test/Species | OECD 201 | NOEC / EC10 |  | µg/L | growth rate |
| *Daphnia magna*, Reproduction Test | OECD 211 | NOEC / EC10 |  | µg/L | applicable endpoint(s) |
| Fish, Early Life Stage Toxicity Test/Species | OECD 210 | NOEC / EC10 |  | µg/L | Applicable endpoint(s) |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC / EC10 |  | µg/L | respiration |

Table 15: Phase IIb studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Phase IIb studies |  |  |  |  |  |
| Bioaccumulation/Species | OECD 305 | BCFxxx  BCFxxx |  | L/kgww  L/kgww | %lipids: X%  %lipids: X% |
| Aerobic and anaerobic transformation in soil  Soil 1 = type (e.g. sandy loam / clay / loamy sand)  Soil 2 = type  Soil 3 = type  Soil 4 = type | OECD 307 | DT50soil1 = d  DT50soil2 = d  DT50soil3 = d  DT50soil4 = d  CO2 (max) = %  NER (max) = %  Transformation products >10% = Y/N,  M1 = %,  DT50 M1: d | | | for all 4 soils  at test end, soilnr  at test end, soilnr  at day X; soil nr |
| Soil Micro organisms: Nitrogen Transformation Test | OECD 216 | NOEC / EC10 |  | mg/kgdw | N transformation |
| Terrestrial Plants, Growth Test/Species | OECD 208 | NOEC / EC10 |  | mg/kgdw | applicable endpoint(s) |
| Earthworm, Acute Toxicity Tests/*E. fetida* | OECD 207 | EC50 |  | mg/kgdw | applicable endpoint(s) |
| Earthworm, Chronic Toxicity Test/Species | OECD 222 | NOEC / EC10 |  | mg/kgdw | applicable endpoint(s) |
| Collembola, Reproduction Test/Species | OECD 232/ISO 11267 | NOEC / EC10 |  | mg/kgdw | applicable endpoint(s) |
| Sediment dwelling organism/Species | OECD 218/219 | NOEC / EC10 |  | mg/kgdw | applicable endpoint(s) |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Where studies have been submitted, comment if the data summary provided by the Applicant adequately reflects data in the actual study reports. If necessary, include information that was omitted but you consider relevant.  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  In addition, contextualise the ERA provided by the Applicant, even in the absence of any studies, with the proposals for the SmPC and PL as regards safe disposal/handling, clearly stating as to whether they are adequate or not.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-know” questions.  <None><Text> |

* + 1. Conclusion on ERA

**Choice of minimal standard sentences suggested for the CONCLUSION in the CHMP AR/EPAR**

1- For active substances that are exempted from assessment according to the guideline (vitamins, electrolytes etc.):

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

2- For substances considered to be potential PBT (persistent, bioaccumulative and toxic) and/or vPvB (very persistent, very bioaccumulative) or with specific concern (e.g. endocrine disruptors), outcome of the specific assessment is added to the standard conclusion on a case-by-case basis.

3- For active substances that remain in Phase I:

PECsurfacewater for <active substance> is below the action limit of 0.01 µg/L and <active substance> is not a PBT substance as log *K*ow does not exceed 4.5.

or for substances already on the market:

<active substance> is already used in existing marketed products and no significant increase in environmental exposure is anticipated

[based on justification].

No data on the environmental risk were available / required therefore a final conclusion on potential risk of <active substance> to the environment cannot be drawn.

4- For active substances that reach Phase II (see table):

<Active substance> is not a PBT substance

or if PBT add a specific conclusion according to the PBT assessment.>

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

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

5- For dossiers requiring additional ERA data:

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of <active substance> to the environment.

[At the time of opinion:]

The Applicant commits to perform the following studies as follow-up measures:

[list of tests to be performed]

[In case some additional studies are requested, please use the following paragraphs.]

<In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points <for further investigation><to be addressed:>

* 1. (Co)-Rapporteur’s overall conclusions on toxicology
     1. Discussion:

The contents of this section should be written so that they can be copy/pasted directly to the CHMP AR/Overview. A self-standing though succinct and focused elaboration might therefore be necessary to allow the reader a comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

Briefly summarise the high-level results of the main studies, emphasising their ability to predict potential adverse events in humans.

Highlight areas of disagreement with the overview (module 2.4) and any issues requiring clarification.

Any deviations from the toxicology programme as stated in the guidelines or from GLP or any absence of required studies should be commented upon.

If it is a bibliographical application or if bibliographical data are used as supportive information, it is particularly important to highlight this.

In general, the rationale for the selection of species/systems, duration and dose/concentrations used in the studies should be provided.

Explanations for the observed effects as well as statements pertaining to the potential relevance for the human use as suggested by the Applicant should be commented and if possible concluded upon.

The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed should be discussed.

Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters such as significant differences in potency between test species and human) should be discussed and the limitations and utility of the non-clinical studies for prediction of potential adverse effects in humans highlighted.

The relevance of the animals in toxicity studies should also be discussed with respect to potential interspecies differences in pharmacology.

Special emphasis should be put on genotoxicity, carcinogenicity and reproductive and developmental toxicity findings. In case of positive genotoxic effects, tumour findings and/or developmental/reproductive toxicity findings, the possible relevance for the human situation should be discussed and if possible concluded upon.

For the carcinogenicity potential consider:

Biological significance of tumour increases, historical data, relation to pharmacological effect, dose-related effects, species-specific differences, mechanistic studies, relationship with genotoxicity and comparison between human and animal exposure etc. As an alternative this section could simply state the main conclusions in which case the text in the “overview” should be elaborated on separately.

Please indicate if additional expertise is needed to assess the human implications. This includes whether there is a need to obtain an Opinion from the PDCO related to data with relevance to the paediatric development.

Comment on the suitability of the proposed SmPC wording. Ensure correspondence between the data submitted and the SmPC (particularly section 5.3 Preclinical safety data but also e.g. sections 4.3 contraindications, 4.6 Pregnancy and lactation, if relevant) and that all information in the SmPC is explicitly assessed and supported by the scientific assessment.

For biosimilars: discuss the results of the toxicology comparability study obtained against the chosen reference medicinal product, if applicable. Discuss if there are differences observed in the final formulation, at quality (e.g. molecular structure, glycosylation profile) non-clinical level (e.g. target receptor binding, functional activity) or PK/PD level that could affect toxicology. Conclude if the submitted toxicology data, if any, support biosimilarity under such circumstances. In the case of biosimilars, an environmental risk assessment is not needed.

<Text>

* + 1. Conclusions:

A very brief summary of the conclusions drawn from the toxicology should be provided here.

<Text>

1. Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP)

Rapporteur’s comments:

(To be filled in by the Rapporteur only)

[Please review Part II: Module SII - Non-clinical part of the safety specification of the RMP of the Applicant.

Comment if non-clinical safety findings have been identified which may be of significant clinical relevance. Refer to the Overall conclusion on Toxicology (section 4.9.); there is no need to repeat the discussion from that section.

For biosimilars: the RMP of the reference product should be followed and cases of divergence (if any) need to be discussed and highlighted in the clinical assessment report.

<Text>

1. List of references

To be completed by the Applicant (if they agreed to pre-fill the template).

Assessors can include additional references if needed.

<Text>