**National Procedure**

**<Project Orbis / Access Consortium>**

**<new MA application>**

**<variation addition/modification of indication>**

**Clinical Assessment Report**

**<Invented name(s)>** **<(Active Substance)>**

**<PL><PLGB>**

**Marketing Authorisation Holder:**

instructions to applicants/assessors for use of this template

**General instructions for the Applicant**

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. Guidance text is provided in blue.

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

Complete all (blue) tables of the template as requested.

The use of additional tables/graphs/figures is encouraged in any of the subheadings. Tables should be included as MS Word tables and not copied as pictures or from PDF. Footnotes should not be forgotten and should include the reference to the relevant eCTD section. Repetition of the same data in the text and tables should be avoided, unless highlighting some qualitative aspects.

Simply copy/paste from the eCTD modules is not acceptable; brief summaries should be provided, allowing for a balanced presentation of “positive” and “negative” findings.

In each relevant subsection, indicate clearly what data are reflected in the proposed SmPC.

Subsections that are not relevant to the product should be identified as not applicable (N/A). Additional subheadings can be included depending on the product (e.g. “Immunogenicity” for a vaccine, “Microbiology” for an antibiotic)

It is recommended to use Verdana, size 9 in the main text and to remove the blue guidance in the application.

**General instructions for the Assessor**

If the Applicant has not agreed to pre-fill the factual sections, this will be done by the Assessor.

Guidance text for assessors is provided in green. The Assessor’s evaluation should be drafted in the boxed sections. If the Assessor does not agree with the Applicant’s presentation of data, this should be described and explained in the Assessor’s Comment box; no change to the data or comment should be included 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.
* *If certain studies have not been conducted or have been replaced with literature data or deviate from the legal and guideline requirements, the Assessor should comment on the acceptability of the Applicant’s justification.*
* *If certain studies are only available as publications, the Assessor should provide a view as to whether these publications allow for an in-depth evaluation of the data.*
* For each type of study, the evaluation should clearly distinguish between main (pivotal) and supportive data.
* The evaluation should focus on salient findings and especially those deficiencies that justify the questions for the Applicant in the MHRA List of Questions (LOQ). In each boxed section, the comments should be followed by the wording of the question(s) with the acronym MO or OC in bold and brackets (see below). The questions are then copied into the LOQ.
* The evaluation should also emphasise findings that need to be reflected in the SmPC. However, comments and edits should be made directly in the attached product information.
* The questions raised in the LOQ should be classified as follows:
* “Major objections” preclude a recommendation for marketing authorisation. The major objection(MO) should start with a statement concerning the pivotal shortcoming and may entail more than one question; in that case, the use of bullet points or subheadings is encouraged. A reference to guidance documents may be useful.

However, the question should not include the details of the deficiencies which have been described in the boxed comments but could refer to the identification of the relevant subsection(s) of the report.

The Assessor is strongly recommended to include a clarification as to what kind of response/action is expected from the Applicant.

* “Other concerns” may impact the benefit/risk evaluation, affect the proposed conditions for marketing authorisation or product information. “Nice to know” questions should be avoided.

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**Administrative information**

|  |  |
| --- | --- |
| Product data |  |
| Product name |  |
| INN or Common Name |  |
| PL<GB> Number |  |
| ATC code |  |
| Pharmaceutical form(s) and strength (s) |  |
| Route of administration |  |
| Proposed indication |  |

|  |  |  |
| --- | --- | --- |
| MHRA Assessment team  |  |  |
|  | Name | E-mail adress |
| Clinical |  |  |
| Clinical Pharmacology |  |  |
| Statistics |  |  |
| RMP |  |  |

|  |  |  |
| --- | --- | --- |
| Timetable |  |  |
|  |  | Date |
| Start of procedure |  |  |
| Initial AR |  |  |
| EAG | Specify: |  |
| CHM |  |  |
| 1st RFI |  |  |
| Responses to 1st RFI |  |  |
| 2nd RFI |  |  |
| Responses to 2nd RFI |  |  |

LIST OF ABBREVIATIONS

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

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

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

CLINICAL CRITICAL ASSESSMENT

1. INTRODUCTION
	1. Type of <application> <application variation>
		1. Legal basis

*Delete the legal bases that are not relevant.*

The legal basis for this Marketing Authorisation (MA) application refers to Human Medicines Regulations 2012:

* full application - Regulation 50 (previously Article 8(3) of Directive 2001/83/EC)
* generic application – Regulation 51 (application for UKMA(NI); regulation 51A (application for UKMA(GB)); regulation 51B (application for UKMA(UK)) (previously Article 10.1 of Directive 2001/83/EC)
* hybrid application – Regulation 52 (application for UKMA(NI)); regulation 52A (application for UKMA(GB)); regulation 52B (application for UKMA(UK)) (previously Article 10.3 of Directive 2001/83/EC)
* similar biological application – Regulation 53 (application for UKMA(NI)); regulation 53A (application for UKMA(GB)); regulation 53B (application for UKMA(UK)) (previously Article 10.4 of Directive 2001/83/EC)
* well-established use application – Regulation 54 (previously Article 10a of Directive 2001/83/EC)
* fixed-combination application – Regulation 55 (previously Article 10b of Directive 2001/83/EC)
* informed consent application - Regulation 56 (previously Article 10c of Directive 2001/83/EC)
* traditional herbal registrations - Regulation 127 (previously Article 16a of Directive 2001/83/EC)
* certificate of homeopathic medicinal products - (called Simplified Registration scheme) - Regulation 103 (previously Article 14(1) of Directive 2001/83/EC)
* national homeopathic products (called the National Rules Scheme) - Regulation 50(6)(g) and Schedule 10 (previously Article 16(2) of Directive 2001/83/EC)

or

The legal basis for this variation application refers to Regulation 65C and Schedule 10A to the Human Medicines Regulations 2012

* + 1. Innovative Licencing and Access Pathway (ILAP)

An Innovation Passport was awarded for <medicinal product (active substance)> in <indication> on <date>

<medicinal product has received a Target Development Profile as part of the ILAP>.

* + 1. Early Access Medicine Scheme (EAMS)

A Promising Innovative Medicine was awarded for <medicinal product (active substance)> in <indication> on <date>

<medicinal product (active substance) was granted a <positive><negative> scientific opinion in <indication> on <date>

* + 1. Procedure route

This is a national application.

This national application is submitted via <ACCESS> <Project Orbis (type A or B)> route in collaboration with the regulatory agencies <XX>.

*If ACCESS route provide input assessment module for each regulatory agency.*

* + 1. <New active substance status>

The Applicant indicates that <INN/common name> is considered to be a <new><known> active substance.

* + 1. <Type II variation>

The MAH submitted to the MHRA on <date> an application for a Type II variation. The following variation was requested:

<Addition of a new therapeutic indication>

<Modification of an approved indication>

The variation requested amendments to the Summary of Product Characteristics(<sectionXX>, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

* + 1. <Conditional marketing authorisation>

<The Applicant is applying for a <conditional marketing authorisation>.

<Product name> was granted a conditional marketing authorisation on <date> for <insert indication>

Outstanding SOB <Insert SOB>

<With this submission, the MAH considers having fulfilled the Specific Obligation (SOB-XX) of the CMA and requests subsequent conversion of the CMA into full approval.>

* + 1. <Marketing authorisation under exceptional circumstances>

<The Applicant is applying for a < marketing authorisation under exceptional circumstances>.

<Product name> was granted a marketing authorisation under exceptional circumstances on <date> for <insert indication>

Outstanding SOB <Insert SOB>

<With this submission, the MAH considers having fulfilled the Specific Obligation (SOB-XX).>

* + 1. Information relating to Orphan market exclusivity

**Orphan designation**

<Product name> has GB OD status in the condition <insert condition> for the indication <insert indication> (GB OD number) since <date>. <A request for separate OD for a new indication in a new orphan condition and 10 years market exclusivity has been submitted>.

<A request for 2 years additional orphan market exclusivity has been submitted for completion of paediatric investigation plan>.

<Product name> has no GB OD status. A request for OD has <not> been submitted with this application>

**Similarity with authorised medicinal products**

<The application included a critical report addressing the possible similarity with authorised orphan medicinal products.>

* + 1. Compliance with PIP

<The application included an MHRA 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>.

<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>.

If the claimed indication does not include paediatric patients, very briefly mention whether a PIP or PIP waiver has been agreed and what paediatric subsets (if any) will be investigated. Briefly summarise the conditions and principal requirements of the paediatric investigation plan with regards to clinical aspects.

<Text>

* + 1. Global regulatory status

*State whether this medicinal product in the proposed indication is authorised or has been refused marketing authorisation/variation in any country. Mention if regulatory procedures have been submitted to any country (including dates) and are ongoing at the time of submission .*

<Text>

* + 1. <Request for additional market protection>

The MAH requests consideration of its application for one year of market protection for a new indication.

The request is based on the the position that <product name> represents a significant clinical benefit in the <new indication> in comparison with existing therapies.

* 1. Description of the product

Briefly describe the product and its mechanism of action. State the proposed indication and posology.

<Text>

***Assessor’s comment***

*<None> <Text>*

* 1. Therapeutic context

Provide background on the medical condition that is necessary to understand the therapeutic context of this application. This section can be abbreviated if the condition is well-recognised. 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 UK 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>

***Assessor’s comment***

*<None> <Text>*

***Assessor’s comment***

*<None> <Text>*

* 1. Compliance with scientific advice

Briefly describe the relevant scientific advice received from MHRA or other regulatory agencies with a very brief summary of the main agreed aspects. If the development programme has diverted from the received advice, please briefly describe the reasons.

<Text>

***Assessor’s comment***

*<None> <Text>*

* 1. GCP aspects

Comment on GCP compliance of the clinical trials supporting this application. Provide a list of GCP inspections and independent audits of the clinical trials, if any.

<Text>

***Assessor’s comment***

***Discuss the need for a triggered GCP inspection as part of the evaluation.***

*<None> <Text>*

1. CLINICAL PHARMACOLOGY

*Complete section III based on eCTD modules 2.7.1 and 2.7.2.*

* 1. Overview of studies

*Complete the following table.*

***Overview of clinical PK and PD studies***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study identifier | Study design | Population | Dosing regimen | Main PK and PD parameters |
|  |  |  |  |  |
|  |  |  |  |  |

*Provide a very high level (1 page max) summary of the clinical pharmacology programme that supports this application.*

<Text>

* 1. Methods
		1. Bioanalytical methods

Provide a brief description of the analytical methods used. The assay validation should be summarised in a table for each method. If applicable, a table showing which method was used for which clinical study should be provided.

<Text>

Pharmacokinetics

<Text>

Pharmacodynamics

<Text>

Immunogenicity

<Text>

***Assessor’s comment***

*Comment on the compliance of the validation (pre-study and in-run) of the analytical methods with the current relevant guidelines. The same applies when other drugs (generally used in the DDI investigation) are part of the PK data package.*

*<Text>*

* + 1. Pharmacokinetic data analysis

Summarise the PK data analysis method and statistical methodology (PK parameters, non-compartmental procedure, CI and acceptance range, etc.). List all models and software used, describe the purpose of the models and place in overall strategy

<Text>

***Assessor’s comment***

*Comment on the appropriateness of the methods used. When non-compartmental (NCA) and modelled approaches have been used, comment on any significant divergence and their justification by the Applicant.*

*<Text>*

* 1. Pharmacokinetics
		1. Absorption

*Briefly summarise data from CTD module 5.3.1 to 5.3.3 as appropriate, (e.g. rate and extent of absorption and involvement of active transport proteins in absorption).*

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance. Comment on involvement of transport proteins in the absorption and BCS classification; comment on any non-linearity in absorption and potential pH dependency in solubility/absorption.*

*<Text>*

* + 1. Bioavailability

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance. Do they support the proposed posology?*

*If absolute bioavailability is unknown, comment on the extent of absorption based on in vitro and other in vivo data (mass-balance, food effect study etc.).*

*<Text>*

* + 1. Bioequivalence

Present data from bioequivalence studies between the formulations used in pivotal clinical studies and the final formulation to be marketed. Other bioequivalence studies may be briefly presented. A table of all the formulations used in the PK development should be included.

<Text>

***Assessor’s comment***

*Are there sufficient data on the commercial product?*

*<Text>*

* + 1. Influence of food

Summarise the data from food interactions studies that used the Phase III and marketing formulations and support the proposed recommendations in the posology section of the SmPC. Recommendations used in pivotal Phase III trials should be described.

<Text>

***Assessor’s comment***

*Has the timing of drug intake in relation to food been sufficiently evaluated? Are the proposed labelling recommendations appropriate?*

*<Text>*

* + 1. Distribution

As per section 5.3.3 of the eCTD, provide data on the volume of distribution, in vitro and ex vivo protein binding of parent drug and pharmacologically active metabolites and blood/plasma ratio. Include data regarding concentration of parent drug and pharmacologically active metabolites in tissues and other body fluids, e.g. cerebrospinal fluid.

If estimations of the volume of distribution are available from non‑compartmental analysis (NCA) and modelled approaches, their concurrence should be checked.

For drugs exhibiting (very) high affinity to plasma proteins, the protein involved should be identified and information regarding the saturation of such binding under therapeutic concentrations should be provided.

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance.*

*Have the methods used for the investigation of in vitro binding to plasma proteins been described and validated? Is the concentration range appropriate in relation to clinically relevant exposures?*

*Have any significant divergence between NCA and models been explained by the Applicant? If extreme estimates have been obtained, has an explanation of their physiological significance been attempted?*

*<Text>*

* + 1. Elimination

As per section 5.3.3 of the eCTD, describe the main pathways of elimination (metabolism, excretion unchanged renally and biliary), clearance, half-life, as well as information on any potential accumulation. Use diagrams if possible to describe elimination pathways and mass balance studies (see example below).



<Text>

***Assessor’s comment***

*Comment on the clinical relevance of the formulation, dose and duration used in the mass balance study. Is the recovery in the mass balance study sufficient as per guideline recommendation (Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*)?*

*<Text>*

* + 1. Metabolism

*As per section 5.3.3 of the eCTD, provide data on identification of metabolites, metabolic routes, enzymes involved in metabolism, extent of metabolism and a proposed metabolic scheme.*

*For the mass balance study, include identification of all metabolites in excreta and the AUC and half-life of parent drug and metabolites in relation to total drug related exposure in plasma. Estimate how much of the AUC of radioactive material has been structurally identified. A figure of plasma concentration-time profile of radioactivity and active substance can be presented here. Include terminal half-life of radioactivity.*

*All in vitro data relevant to metabolism should be reported here, irrespective of the origin of the materials used.*

*Relevant subheadings could be added, including inter-conversion (for chiral products), pharmacokinetics of metabolites, and* *consequences of possible genetic polymorphism (if polymorphically expressed enzymes are involved in the metabolism).*

<Text>

***Assessor’s comment***

*Comment on the plausibility of the elimination pathway as presented by the Applicant. Comment on the metabolites that can be considered major (contributing to ≥10% of total drug-related exposure; Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*).*

*Comment on the estimations of the contribution of metabolites to efficacy and safety taking into account unbound exposure, pharmacological activity data, and distribution characteristics to target tissue(s).*

*Inter-conversion*

*Comment on the possible clinical consequences of inter-conversion and whether the Applicant has adequately assessed the risk.*

*For chiral substances where the enantiomers exhibit different PK and PD, consider the need for a chiral analysis method and evaluation of the PK for the separate enantiomers.*

*Pharmacokinetics of metabolites*

*Is any of the information provided about metabolites of concern? Are any additional investigations needed? Have the pharmacokinetics of parent drug and active metabolites been sufficiently documented in special populations?*

*Consequences of possible genetic polymorphism*

*Comment on the need for specific investigations in rapid and slow metabolisers and subsequent dose adjustment. Comment on the need and practicability of genotyping and/or phenotyping of patients prior to treatment in line with any Applicant’s proposal.*

*Does the SmPC (sections 4.2, 4.3, 4.4, 4.5 etc.) appropriately reflect the information relevant to a pharmacogenetic subpopulation?*

*<Text>*

* + 1. Dose proportionality and time dependency

#### Dose proportionality

Provide information on dose proportionality after a single dose and at steady state. Describe whether or not the PK of the product is linear. Describe the reason for any non-linearity (e.g. saturation of elimination, transport proteins, absorption, limited solubility, concentration dependent protein binding) and the consequences of the non-linearity (e.g. for dosing recommendations and the design of interaction studies).

<Text>

***Assessor’s comment***

*Comment on the reasons and consequences for any non-linearity. Are the proposed dosing recommendations adequate? Have interaction studies been designed appropriately?*

*<Text>*

#### Time dependency

Provide data on systemic exposure after single and multiple dose administration of the therapeutic dose and evaluation of time dependency. Any accumulation after repeated dose should be described. When relevant, add information regarding the impact of anti-drug antibodies (ADAs) on PK (if required, use a separate heading).

<Text>

***Assessor’s comment***

*If PK is time dependent, comment on the reasons and potential consequences (e.g. for dosing and drug-drug interactions).*

*<Text>*

* + 1. Intra- and inter-individual variability

*Provide data on intra- and inter-individual variability in pharmacokinetic parameters, preferably in the target population.*

<Text>

***Assessor’s comment***

*Are intra- and inter-individual variabilities sufficiently addressed for the posology determination?*

*<Text>*

* + 1. Pharmacokinetics in the target population

If pharmacokinetics have mainly been documented in the target population and not in healthy volunteers, this section can simply cross-refer.

Provide available PK data of parent compound and pharmacologically active metabolites in the target population with special emphasis on differences from healthy volunteers and variability in patients.

PopPK methodology and results should be presented, e.g. covariate analysis.

<Text>

***Assessor’s comment***

*If a modelled approach is used to inform the PK in a special group, comment on the robustness of the data to support a claim with high regulatory impact such as a contraindication, dose adjustment or precaution of use.*

*<Text>*

* + 1. Special populations

*Populate these sections with data from CTD module 5.3.3.3, Intrinsic factor PK study reports, and CTD module 5.3.3.5, PopPK study reports. Statements made after consideration of these data should be reflected in the product information.*

#### Impaired renal function

If no dedicated study has been performed this should be justified. Data (from literature or PopPK covariate analysis) should be summarised to describe the relationship between renal function and exposure. Generally, data should be evaluated using absolute GFR (ml/min) and not body size-adjusted GFR (ml/min/1.73 m2). For highly protein bound drugs data on unbound exposure should be presented.

<Text>

***Assessor’s comment***

*Is a dedicated study on renal impairment available? If so, is the method for grading subjects with renal impairment consistent with the recommendations in the proposed SmPC?*

*If no such study is available, is the lack of data adequately reflected in the SmPC?*

*<Text>*

#### Impaired hepatic function

If no dedicated study has been performed this should be justified. Data (from literature or PopPK covariate analysis) should be summarised to describe the relationship between hepatic impairment and exposure. For highly protein bound drugs data on unbound exposure should be presented.

<Text>

***Assessor’s comment***

*Is a dedicated study on hepatic impairment available? If so, is the method for grading subjects with hepatic impairment consistent with the recommendations in the proposed SmPC?*

*If no such study is available, is the lack of data adequately reflected in the SmPC?*

*<Text>*

#### Gender

Provide a brief statement on whether gender differences were investigated in a clinical study and/or as a covariate on drug PK and whether it was found to be of significance.

<Text>

***Assessor’s comment***

*If any gender differences have been noted, are they appropriately reflected in the SmPC?*

*<Text>*

#### Ethnic factors

Provide any data that outline potential differences in PK based on ethnic factors. Discuss whether the numbers of subjects of each ethnicity are sufficient to draw appropriate conclusions.

<Text>

***Assessor’s comment***

*If any differences related to ethnicity have been noted, are they appropriately reflected in the SmPC?*

*<Text>*

#### Weight

Provide any data that outline potential differences in PK based on body weight, with particular focus on obese and underweighed subjects.

<Text>

***Assessor’s comment***

*If any differences based on weight have been noted, are they appropriately reflected in the SmPC?*

*<Text>*

#### Elderly

Specific PK studies/data in older subjects should be presented by age range (65-74, 75-84, and 85 plus years) with the number of subjects in each category. If PK in older people is likely to be altered, e.g. due to renal impairment, the need for dose adjustment should be discussed.

<Text>

***Assessor’s comment***

*If any differences in the elderly population have been noted, are they appropriately reflected in the SmPC?*

*<Text>*

#### Paediatric population

*If the claimed indication includes paediatric patients, state whether studies in paediatric subjects have been conducted or not. In case extrapolation is used to support a paediatric indication, available data on exposure supporting the indication should be reported here.*

<Text>

***Assessor’s comment***

*If a paediatric indication is claimed based on extrapolation, comment on the uncertainties of the extrapolation and whether use in the paediatric population is appropriately reflected in the SmPC.*

*Refer to published guidelines on the use of extrapolation to paediatrics:*

[*https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1\_en.pdf*](https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf)

[*https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers*](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers)

*<Text>*

* + 1. Pharmacokinetic interactions studies

#### In vitro

Present all in vitro experiments to address interaction risks using appropriate tables based on data from CTD module 5.3.2 in vitro studies.

State for which transporters and enzymes the active substance is a substrate.

Complete the following tables.

**Cut-offs for the evaluation of interaction potential**

|  |  |  |  |
| --- | --- | --- | --- |
|  | 50Cmax(u)a(µM) | 25Inlet Cmax(u)a(µM) | 0.1dose/250 mlb(µM) |
| Parent drug |  |  |  |
| Metabolite 1 |  | NA | NA |
| Metabolite 2 |  | NA | NA |

a Multiple dose Cmax, xxx mg dose (study YYY)

b Based on a xxx mg dose

NA - Not applicable

<Text>

***Summary of in vitro enzyme inhibition***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Enzyme | Substrate | Competitive inhibition | TDI | Positive signal to evaluate further |
|  |  | Ki\* (μM) | KI (μM) | Kinact (min-1) | Yes/No |
| CYP1A2 |   |   |   |   |   |
| CYP2B6 |   |   |   |   |   |
| CYP2C8 |   |   |   |   |   |
| CYP2C9 |   |   |   |   |   |
| CYP2C19 |   |   |   |   |   |
| CYP2D6 |   |   |   |   |   |
| CYP3A4 |   |   |   |   |   |

<Text>

***Summary of in vitro transporter inhibition***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Transporter | Substrate | In vitro system | Ki\* (μM) | Positive signal (Yes/No) |
| P-gp |   |   |   |   |
| BCRP |   |   |   |   |
| OATP1B1 |   |   |   |   |
| OATP1B3 |   |   |   |   |
| OAT1 |   |   |   |   |
| OAT3 |   |   |   |   |
| OCT2 |   |   |   |   |
| OCT1 |   |   |   |   |
| MATE1 |   |   |   |   |
| MATE2 |   |   |   |   |
| BSEP |   |   |   |   |

\* If IC50 is used instead of Ki a justification should be provided (including linearity, choice of substrate concentration etc.)

<Text>

***Assessor’s comment***

*Comment on study designs including concentration ranges, positive controls and stability of the test compound. Comment on in vivo relevance of observed inhibition.*

*If the Applicant has presented IC50 and not Ki data, assess the justification and consider if e.g. use of IC50/2 as an estimate for Ki is appropriate.*

*If the RIS model or mechanistic static model is used, the qualification of the system and its validity for the specific study should be assessed along with the study results.*

*<Text>*

#### In silico

Discuss the role of PBPK models and the results. How do simulated data compare to in vivo data?

Discuss confidence in in–silico predictions based on submitted or literature data and the impact on dosing recommendations. Is the PBPK platform qualified for the intended purpose?

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling.*

*<Text>*

#### In vivo

Briefly describe the clinical interaction studies performed.

Complete the following table.

**Overview of clinical DDI studies**

|  |  |  |
| --- | --- | --- |
| Comparison | Substance Ratio, as Percent (90% CI) | Dosing Recommendation |
|  | Cmax | AUCinf |  |
| Victim |
| Effect of co-administration with X |  |  |  |
| Effect of co-administration with Y |  |  |  |
| Perpetrator |
| Effect on substance X |   |   |   |
| Effect on substance Y |   |   |   |

<Text>

***Assessor’s comment***

*Comment on the study designs and mechanistic predictions of other interacting drugs based on the results. Refer to Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*).*

*Have “positive” results in in vitro inhibition/induction studies been followed up in vivo with appropriate probe substrates?*

*Do PBPK modelling or PopPK modelling support in vivo data? Do PBPK and PopPK suggest additional PK interactions?*

*Are there any other potential clinically relevant interactions, e.g. inhibition or induction of enzymes/transporters that have not been studied? Are additional in vitro, in vivo or in silico drug interaction studies needed and can these be done post-authorisation?*

*Do exposure-response or PK/PD analyses together with clinical data suggest that PK interactions may change the benefit/risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments or therapeutic drug monitoring?*

*Is the interaction potential different in certain subgroups intended for treatment (e.g. poor metabolisers, patients with RI etc)?*

*<Text>*

* + 1. Exposure relevant for safety evaluation

Summarise the exposure expected in the target population at steady state. Describe whether there is any specific sub-population with increased or reduced exposure and what consequences are to be expected.

<Text>

***Assessor’s comment***

*Does the exposure in the target population support the proposed posology? Does the SmPC recommend posology modifications in populations with reduced or increased exposure?*

*<Text>*

* 1. Pharmacodynamics
		1. Mechanism of action

Describe the mechanism of pharmacodynamic action in relation to the clinically desired primary pharmacological (therapeutic) effects (primary pharmacodynamic action). The choice of the PD biomarkers should be justified in relation to the mechanism of action. In addition, the mechanism of potential secondary pharmacodynamic actions should be described.

Describe if clinical PK/PD models provide further insight on the proposed mechanism of action. Consistency shown in the clinic with the non-clinically identified mechanism of action and mechanistic modelling should be described.

<Text>

***Assessor’s comment***

*Comment on the validity of the human models and their relevance with regard to the therapeutic effects.*

*Are the biomarkers used relevant? Has the mechanism of action been sufficiently characterised? Is the description in the SmPC appropriate?*

*<Text>*

* + 1. Primary pharmacology

Summarise the studies on the effects of the drug in relation to its desired therapeutic indication/target. The design of the studies should be discussed including PD endpoints, the clinical relevance of biomarkers, the range of doses tested and the number of individuals/time points of PK and PD sampling.

Summarise also the results of studies that have investigated the covariate effects on primary pharmacology, e.g. effects of age or genetic polymorphism on PD (or PK/PD) relationships.

<Text>

***Assessor’s comment***

*Comment on modelling and simulation approaches used to link dose, exposure and PD, including covariate effects. Consider whether efficacy might be reduced in different populations, e.g., the older adult population due to PD changes.*

*Is there consistency of assumptions on primary pharmacology across non-clinical development and throughout clinical development?*

*<Text>*

* + 1. Secondary pharmacology

Describe the secondary pharmacology. Include in this section the general features of tolerability in healthy volunteers with regard to secondary pharmacology on relevant dynamic endpoint studies, e.g. 24-hour blood pressure, biochemistry, virus levels, ECG, EEG etc.

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling (indication, posology or any other section of the SmPC).*

*<Text>*

* + 1. Pharmacodynamic interactions with other medicinal products or substances

Describe interactions with other medicines and any kind of substances with an impact on the dosing recommendations due to a PD interaction. The proposed text for the SmPC with precautions or warnings should also be discussed here.

<Text>

***Assessor’s comment***

*Have potential interactions with other medicines (including herbal remedies if relevant) been sufficiently characterised? Are the proposed recommendations in the SmPC appropriate?*

*Note: Pharmacokinetic and pharmacodynamic interactions should be clearly separated.*

*<Text>*

* + 1. Genetic differences in PD response

Describe any genetic differences in PD response as well as potential differences in the paediatric population (e.g. due to maturation).

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling.*

*<Text>*

* 1. Pharmacokinetics-Pharmacodynamics (PK/PD)
		1. Relationship between plasma concentration and effects/safety

Briefly summarise data from CTD module 5.3.4 on PK/PD in healthy volunteers and patients.

If available, drug-exposure-response and PK/PD approaches based on data across studies should be described here. Indicate if these analyses were used to define the time course of drug effects, the range of doses tested in early clinical development and whether the selection of dose(s) and study duration for Phase III were supported by these analyses. Present the covariate effects on PK/PD and drug-exposure-response relationship.

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling.*

*Do exposure-response or PK/PD analyses together with clinical data suggest that unexplained or explained variability in PK may change the benefit/risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments in special populations or therapeutic drug monitoring or a post-authorisation safety or efficacy study.*

*<Text>*

* + 1. Evaluation and qualification of PK/PD models

Describe the rationale and development of PK/PD models, exposure-response model and simulation methods together with all covariate analyses (e.g. hepatic and renal impairment, gender, ethnic factors, prior use of medications) taken into account. Describe model evaluation.

Summarise PK/PD analyses in healthy subjects as well patients. Describe any effect on potential biomarkers or disease progression.

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they influence the indication and posology.*

*<Text>*

* 1. Immunological events

Describe antibody formation and their impact onPK, PD, efficacy and safety (e.g. neutralising antibodies, auto-antibodies, and species-specific antibodies.).

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling.*

*<Text>*

* 1. Dose justification

Provide a summary of how PK/PD were used to select the doses throughout the development programme, including reference to approaches based on non-clinical data to determine the appropriate dose in humans, if relevant.

<Text>

***Assessor’s comment***

*Comment on the strength of the Applicant’s justification for the proposed posology, including adjustments for specific populations and coadministration with other medicines.*

*<Text>*

* 1. Overall assessment of clinical pharmacology
		1. Discussion

*This should be a brief summary of the key findings and should focus on the strengths and weaknesses of the PK and PD data submitted. It is based on the boxed comments of the Clinical Pharmacology section but should not be a copy/paste of all these comments. This discussion should emphasise the main areas of uncertainty that should be addressed by the Applicant (LOQ).*

<Text>

* + 1. Product information

This should be a general assessment of the suitability of the proposed SmPC, specifically sections 4.2, 4.5 and 5.2. Comments and edits should be made directly in the attached product information.

<Text>

* + 1. Conclusions

This should be a general statement on the quality/validity and relevance of the Clinical Pharmacology documentation. It should conclude whether an MO is raised (and on what ground) or only OCs.

<Text>

1. CLINICAL EFFICACY

*Complete section 3 based on eCTD modules 2.5, 2.7.3 and 5.3.5.*

* 1. Clinical development

*Complete the following tabular overview of the relevant clinical studies.*

***Overview of clinical efficacy studies***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Enrolment statusStart dateTotal enrolment/ enrolment goal | DesignControl type | Study & control drugsRoute of administration; posology; treatment duration | Population |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

***Assessor’s comment***

*Comment on the general acceptability of the development plan to support the claimed indication.*

*<Text>*

* 1. Dose response study(ies)

Briefly describe the study design of studies contributing to the selection of dose(s) used in the pivotal studies. Briefly justify the sample size, number and range of studied doses and endpoints.

Outline the results and how they contributed to the selection of the dosing regimen, characterisation of exposure/response relationship and proof of concept. However, avoid duplication of data already covered in the Clinical Pharmacology section and use cross-references.

If dose response studies are lacking, provide a justification for the choice of dose in this section.

If the pivotal trial has a dose-escalation phase, this should simply be mentioned here and the design should be described in section 4.3.

<Text>

***Assessor’s comment***

*Comment on the Applicant’s approach to dose selection. Have sufficient exposure/response studies and/or modelling been carried out to support the proposed posology?*

*<Text>*

* 1. Main study(ies)

Complete the sections below for each pivotal study presented.

In the case of multiple pivotal Phase III studies with similar methodologies a summary of the common methodology is preferred. Individual features of each study may then be described under the heading of each individual study. As for the methods, results can be reported jointly (each study results side by side and pooled but not presented only as pooled results) or separately for each trial (depending on the degree of similarity in study designs and outcomes). Justification for combining results should be provided together with the implication for the interpretation of the data.

* 1. <Study #1 identifier>

|  |  |
| --- | --- |
| Study identifier |  |
| Identification number(s) |  |
| Study title |  |
| Location in eCTD |  |

* + 1. Study design

Describe the main design features of the study. This section should be in line with ICH M11 protocol template

[*https://database.ich.org/sites/default/files/ICH\_M11\_Template\_Step2\_2022\_0904.pdf*](https://database.ich.org/sites/default/files/ICH_M11_Template_Step2_2022_0904.pdf)

<Text>

***Figure: Study schema***

<Figure>

#### Study population

Describe the main inclusion/exclusion criteria and geographical location. If a companion diagnostic was used to screen participants at entry, describe it here.

<Text>

#### Trial intervention

Describe the intervention for each arm (experimental, placebo, active comparator, sham comparator)and period of the trial. Indicate whether an additional product was to be provided as part of the trial and its intended use (background intervention, challenge agent, diagnostic, etc)

<Text>

#### Randomisation and blinding

<N/A><Text>

#### Concomitant and rescue therapies

List permitted or prohibited concomitant medications. If relevant, describe any rescue therapies that could be used during the course of the trial.

<Text>

#### Trial assessments

*Describe the methods and schedule for the assessment of efficacy, including blood test, CT scan, MRI, biopsy, functional measurements, patient reported outcomes, etc... If applicable, provide description of planned or unplanned changes in the conduct of the study.*

<Text>

***Assessor’s comment on study design***

*Is the design of the pivotal studies appropriate (placebo- or active-randomised trials) and in line with regulatory guidance? If not, is the justification acceptable?*

*Are the selection criteria of the patient population appropriate to define the target population and claimed indication?*

*Is the choice of comparator consistent with current therapeutic guidelines and clinical practice?*

*Are the randomisation and blinding methods acceptable?*

*Is the duration of the study appropriate considering scientific knowledge and regulatory guidance?*

*Are the assessment methods sufficient for the intended purpose? Are they «clinically validated»? Is the assessment consistent across treatment arms, and if not, is this justified?*

*Does the design of the planned study address the indication/posology claimed by the Applicant?*

*Do any planned/unplanned changes in the study conduct potentially impact the interpretation of the results?*

*<Text>*

* + 1. Objectives, endpoints and estimands

#### Primary objective

Describe the specific objective and hypothesis. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority). In case of non-inferiority or equivalence, state the pre-defined non‑inferiority or equivalence margin(s) with justification.

<Text>

#### Estimand<s> for the primary objective

*Complete the following table.*

***Estimands for primary objective***

|  |  |
| --- | --- |
| Population | Choose those that apply and delete the rest<Patients with [condition and applicable specifiers] who would encounter the Intercurrent Event of [intercurrent event] if assigned to [treatmentName].><Patients with [condition and applicable specifiers] who would not encounter the Intercurrent Event of [intercurrent event] <if assigned to [treatmentName].><Patients with [condition and applicable specifiers] who would encounter the Intercurrent Event of [intercurrent event] under any treatment assignment.> <Patients with [condition and applicable specifiers] who would not encounter the Intercurrent Event of [intercurrent event] under any treatment assignment.>  |
| Treatment condition<s> | Choose the statement that applies (modifications allowed) and delete the rest<Assignment to [treatmentName], regardless of discontinuation, compared to assignment to [comparatorName], regardless of discontinuation.><Assignment to [treatmentName] and [additional medication] as needed, regardless of discontinuation and use of additional medications, compared to assignment to [comparatorName] and [additional medication] as needed, regardless of discontinuation and use of additional medications.><Assignment to [treatmentName], regardless of discontinuation and added to [background medication] compared to assignment to [comparatorName], regardless of discontinuation, added to [background medication].><Assignment to [treatmentName] in the hypothetical scenario of no discontinuation compared to assignment to [comparatorName] in the hypothetical scenario of no discontinuation.><Assignment to [treatmentName] and [additional medication] as needed, in the hypothetical scenario of no discontinuation compared to assignment to [comparatorName] in the hypothetical scenario of no discontinuation and use of additional medications.><Assignment to [treatmentName] and [additional medication] as needed, in the hypothetical scenario of no discontinuation, added to [background medication], compared to assignment to [comparatorName], regardless of discontinuation, added to [background medication].> |
| Endpoint (variable) | [name of the variable or outcome to be observed from every participant] at [timepoint] <or before the occurrence of the [intercurrent event]>  |
| Population-level summary | [Population-level summary, e.g. difference in means] |
| Intercurrent events and strategy to handle them |
| <Intercurrent event 1> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> <Other> |
| <Intercurrent event n> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> <Other> |

*Provide a brief description in plain language of the estimand(s), intercurrent events and strategies applied. If applicable, substantiate the use of a surrogate endpoint.*

<Text>

***Assessor’s comment***

*Comment on the definition and clinical relevance of the primary endpoint(s). Comment on the acceptability of any composite endpoint and its domains, if applicable. Comment on the justification and validity of any surrogate endpoint, if applicable.*

*Comment on the justification of the statistical hypothesis, estimands and intercurrent events.*

*<Text>*

#### <Secondary> <Tertiary> objective

*Refer to primary objective.*

<Text>

#### Estimand(s) for the <Secondary> <Tertiary> objective

*Refer to primary objective. Use the above table at least for key secondary estimand(s).*

<Text>

***Assessor’s comment***

*Refer to primary endpoints.*

*<Text>*

* + 1. Statistical methods

#### Planned analyses

Briefly summarise the following:

. analysis sets

. main analysis methods for primary and important secondary endpoints

. statistical tests and estimation methods in relation to estimands defined above, where applicable

. methods applied for multiplicity control, where applicable (e.g. across endpoints or interim analyses)

. handling of missing data

. sensitivity or supplementary analyses

If real world data (RWD) are used to provide an external control arm it should be described here.

<Text>

#### Planned subgroup analyses

<Text>

#### Sample size determination

<Text>

#### Error probabilities, adjustment for multiplicity and interim analyses

<Text>

#### Changes from protocol-specified analyses

Describe any changes made to the statistical analysis and/or any ad hoc or unplanned analysis.

<Text>

***Assessor’s comment on the statistical methods***

*Comment on the validity of the planned analyses and of any changes (planned or post hoc). Is the statistical analysis appropriate to address the proposed hypotheses? Was the planned sample size followed?*

*In case of RWD use, refer to MHRA guidance* [*MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions - GOV.UK (www.gov.uk)*](https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions)

*<Text>*

* + 1. Data quality assurance

*Briefly describe the quality assurance systems in place, e.g. training, monitoring, data management and analyses, audits.*

<Text>

***Assessor’s comment***

*Comment on the acceptability of the measures put in place by the Applicant. If there is any area of concern, discuss the potential need for a GCP inspection (cross-refer to section 1.6).*

*<Text>*

* + 1. Results

#### Changes in the planned conduct of the study

Describe and justify any substantial protocol amendments implemented during the conduct of the study, including the dates at which they were introduced in relation to the trial phase (e.g. prior to recruitment start, during recruitment, during follow-up, prior to/after interim analyses/database lock/unblinding). Note that changes to the statistical analysis should be described in section 4.3.1.3.5.

Provide information on protocol compliance and GCP inspection findings, if applicable.

<Text>

***Assessor’s comment***

*Comment on the impact of protocol amendment(s) and protocol compliance on the validity and interpretation of the results.*

*<Text>*

#### Participant flow and numbers analysed

Include key dates of the study (start/end of trial, start/end of recruitment, follow-up, database lock date, interim/final analyses). Include summary of number of patients per centres/countries. Median follow-up at data cut-off date should be presented.

Describe the flow of the progress of study participants through all the phases of the trial using the example of diagram below with minimal textual explanation.

Specifically, for each treatment arm, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary endpoint, e.g.:

* Enrolment (No. subjects screened; No. excluded and reasons for screening failure)
* Allocation (No. randomised, No. started allocated treatment, No. that did not start allocated treatment and reasons)
* Follow-up (No. treatment discontinuations and reasons; No. study discontinuations and reasons – Note that treatment and study discontinuations should be clearly distinguished)
* Analysis (No. included into set for analysis of primary estimation; No. excluded and reasons).

Describe criteria for rescue treatment and for early escape if relevant for the understanding of the interpretation of the results.

**Figure: Participant flow *(Use and amend as appropriate)***

Randomised (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= )

. Discontinued study (give reasons) (n= )

. Discontinued intervention (give reasons) (n= )

**Allocated to intervention (n= )**

. Received allocated intervention (n= )

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

. Discontinued study (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**

**Screening**

**Number analysed**

Provide the number of participants per arm in each analysis dataset (ITT, mITT, PP, etc…) and the number of patients having an intercurrent event for the primary objective (see Estimand section) according to each particular intercurrent event. A tabulated summary is preferred.

Clarify what instances result in missing data.

Specify how patients and data points were included in or excluded from the analysis with a justification based on the selected strategy and estimator.

Provide a tabulated summary of protocol violations/deviations.

<Text>

***Assessor’s comment***

*Comment on the proportions and reasons for screen failures and discontinuations as well as their potential impact on the validity and interpretation of the results. Comment on any imbalance in participant flow across treatment arms.*

*<Text>*

#### Baseline data

Provide a tabular summary of demographic and baseline clinical characteristics by treatment arm.

<Text>

***Assessor’s comment***

*Does the study population reflect the claimed indication? Comment on the homogeneity or imbalance(s) across treatment arms.*

*<Text>*

#### Endpoints and estimation

Summarise the study results (with their estimated precision) for the primary, key secondary and other important endpoints using tables and figures. For secondary or other endpoints, the focus should be on those that provide additional relevant information, not those highly correlated to the primary endpoint. Text should be mainly restricted to the critical discussion of the results.

<Text>

#### Pre-defined and ad hoc important subgroup analyses

Summarise the results of all pre-defined subgroup analyses and ad hoc important subgroup analyses using tables and figures. Text should be mainly restricted to the critical discussion of the results.

<Text>

#### Ancillary analyses

This section should only be used in cases where additional analyses not described in the previous sections were performed, e.g. post hoc analyses.

Modelling and Simulation (M&S) analyses (e.g. PopPK, PopPK/PD) that may support use in a target population different from the study population should be addressed here. Reference to the relevant pharmacology sections in combination with a brief statement on what group of patients should be additionally covered may be included.

<N/A><Text>

***Assessor’s comment on the efficacy results***

*Are the data sufficient to demonstrate an effect of the intervention at the proposed regimen in the target population? If not, what additional data would be needed to determine an effect?*

*Comment on the clinical relevance of the observed effects and whether they support the claimed indication at the recommended dose.*

*<Text>*

* 1. <Study #2 identifier>

In case of multiple pivotal studies, please copy and paste in this section the whole of the headers for section 4.3.1. Repeat this process as per the number of pivotal studies submitted in the dossier.

* 1. Clinical studies/subgroup analyses in special populations

Include in this section special studies, e.g. in children, in the elderly, in pregnant or lactating women and in patients with renal or hepatic impairment. Describe these studies as suggested for the main studies including considerations on dose adjustments. If a paediatric indication is sought, briefly refer to the PIP. If the disease/condition is prevalent in a specific sub-population of subjects, any specific data in those subjects should be presented or the absence of such studies should be justified.

Complete the following table.

**Overview of clinical studies in special populations**

|  | Controlled Trials | Uncontrolled trials |
| --- | --- | --- |
| Renal impairment\* patients (Subjects number /total number) |  |  |
| Hepatic impairment\*\* patients (Subjects number /total number) |  |  |
| Paediatric patients <18 years (Subjects number /total number) |  |  |
| Age 65-74(Subjects number /total number) |  |  |
| Age 75-84(Subjects number /total number) |  |  |
| Age 85+(Subjects number /total number) |  |  |
| Other(Subjects number /total number) |  |  |

\* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

\*\* Hepatic impairment is defined as having Child-Pugh score B or C

<Text>

***Assessor’s comment***

*Comment on the results and strength of evidence/relevance and whether they support the proposed labelling.*

*Comment on the relevance of subgroup data for the assessment of efficacy. Refer to the* [*Guideline on the investigation of subgroups in confirmatory clinical trials*](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf)*.*

*<Text>*

* 1. In vitro biomarker test for patient selection (companion diagnostic)

If applicable, provide the scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism, relation to treatment effect, etc).

Describe the analytical method including assay platform, specimens, and read-out method. Describe how the assay was validated for suitability, robustness, accuracy, specificity, sensitivity and linearity.

<N/A><Text>

***Assessor’s comment***

*Comment on the scientific rationale for selecting the proposed subset of patient population and whether the assay is appropriate for patient selection.*

*Note: this is not the “assessment of suitability” of a companion diagnostic, as performed by a Notified Body.*

*<Text>*

* 1. Analysis performed across trials (pooled analyses and meta-analysis)

This section should only be used for combined analyses from several trials, as included in the Integrated Summary of Efficacy.

State the criteria (rationale and potential bias) used for these analyses and summarise their results using tables and figures.

<N/A><Text>

***Assessor’s comment***

*Comment on the results and* *strength of evidence/relevance and whether they support the proposed labelling.*

*<Text>*

* 1. Supportive study(ies)

Summarise any relevant studies not already included in the previous sections.

If any Real-World Data (RWD) were used to support SmPC claims, describe the data sources used and justify their suitability to answer the research questions, includy brief results of feasibility analyses.

Note: If RWD were used to provide an external control arm they should be described as part of the corresponding pivotal study.

<N/A><Text>

***Assessor’s comment***

*Comment on the* *added value of the supportive studies, as well as their possible limitations (e.g. data representativeness, quality, missingness, risk of confounding and bias, lag time, suitability based on study design).*

*Comment on the strength of evidence/relevance of the supportive studies and whether their inclusion and associated claims are acceptable in the SmPC.*

*In case of RWD use, refer to* [*CHMP guideline on registry-based studies*](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf) *and MHRA guidance* [*MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions - GOV.UK (www.gov.uk)*](https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions)

*<Text>*

* 1. Patient and healthcare provider engagement

Briefly summarise if there was patient and/or HCP engagement that had an impact on the product clinical development (e.g. specific guidance from HCPs/patients on the use of endpoints, assessments, disease impact, PROs, etc.)

<N/A><Text>

***Assessor’s comment***

*Comment on the relevance of any engagement, its added value, possible limitations and possible impact on SmPC wording.*

*<Text>*

* 1. Overall assessment of clinical efficacy
		1. Discussion

*This should include a brief summary of the key efficacy findings and a critical discussion focusing on the strengths and weaknesses of the whole efficacy package submitted to inform the benefit/risk assessment of the product.*

*It is based on the boxed comments of the Clinical Efficacy section but should not be a copy/paste of all these comments. This discussion should emphasise the main areas of uncertainty that should be addressed by the Applicant in response to the LOQ.*

Design and conduct of the clinical studies

*Discuss the Applicant’s choice of design, comparator, population, endpoints, and statistical analyses in line with scientific knowledge and regulatory requirements.*

*Discuss the conduct of the study, impact on the validity of the results and possible need for a GCP inspection.*

<Text>

Efficacy data and additional analyses

*Include a discussion on the following aspects:*

* *precision of the effect estimates*
* *internal and external validity of trial findings*
* *dose-exposure-efficacy response (D-E-R) relationship and intrinsic/extrinsic factors affecting this relationship*
* *specific considerations for special populations*
* *if applicable, any justification for waiving certain studies or replacing original studies by literature data*
* *if applicable, request for additional analyses/data (e.g. longer term/follow up data)*

<Text>

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

*Describe the data missing from Module 5, why they are missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. what data are required.*

[*https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice#guidance-for-great-britain-conditional-marketing-authorisation-applications*](https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice#guidance-for-great-britain-conditional-marketing-authorisation-applications)

*The following statement should be used:*

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

<Text>

* + 1. Product information

This should be a general assessment of the suitability of the proposed SmPC. Comments and edits should be made directly in the attached product information.

Mention briefly if change in section 4.1 is requested (unless minor editorial) as Major Objection and refer to previous section.

Note: Section 5.1 of the SmPC should present information relevant to the prescriber and other HCPs, to support their decision to prescribe the product for an individual patient in the context of the approved therapeutic indication(s). This information can be used by the prescriber to communicate with the patient about treatment objectives and expected benefits.

It is absolutely essential that information in section 5.1 is concise, clear, and limited to data relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified endpoints in the major trials. If information from subgroup or post hoc analyses are considered clinically relevant, it should be identified as such and reflect the limited robustness of the observations. The magnitude of effects should be described using relative and absolute values with their precision.

Section 5.1 may provide further information on the approved indication by summarising details on the target population (e.g. disease stage) with cross reference in section 4.2.

The use of summary tables or figures is preferred for the presentation of efficacy results. The same data should not be described twice, in tables/figures and in the text.

The wording should be objective and not promotional. For example, the use of adjectives and adverbs such us “very strong” effect should be avoided, as well as value statements like “clinically relevant".

<Text>

* + 1. Conclusions

This should be a general statement on the quality/validity and relevance of the Clinical Efficacy documentation. It should conclude whether an MO is raised (and on what ground) or only OCs and whether additional studies are required.

<Text>

1. CLINICAL SAFETY

*Complete section 5 based on eCTD modules 2.5, 2.7.4 and 5. Definitions of adverse events should be in line with ICH E2A.*

* 1. Safety data collection

Describe the methods used to collect safety data, their schedules, the duration of follow-up. If safety data are pooled, describe the rationale and method for pooling and analyses.

<Text>

***Assessor’s comment***

*Comment on the suitability and reliability of the safety data collection.*

*<Text>*

* 1. Patient exposure

List clinical studies contributing to safety; cut-off dates, median (range) duration of treatment and duration of follow-up should be stated.

Numbers and main characteristics of included patients (e.g. age, stage/severity of disease) and healthy subjects should be presented in the table below. Paediatric patients should be presented separately by age groups, as appropriate. Any information on exposure >12 months should be provided.

**Overview of patient exposure (cut-off: …)**

|  | Patients enrolled | Patients exposed\* | Patients exposed to the proposed dose range | Patients with long term\*\* safety data |
| --- | --- | --- | --- | --- |
| Blinded studies (placebo-controlled) |  |  |  |  |
| Blinded studies (active-controlled) |  |  |  |  |
| Open studies |  |  |  |  |
| Post marketing |  |  |  |  |
| Compassionate use |  |  |  |  |

\* Received at least 1 dose of active treatment

\*\* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

*A table(s) with summary of study treatment for safety population including duration of treatment/treatment intervals/dose intensity/dose modifications is encouraged.*

***Assessor’s comment***

*Comment on the suitability of the safety database (size, duration of follow-up, target population) and discuss any limitations in relation to the intented use of the product and proposed target population.*

*<Text>*

* 1. Adverse events

The information should be presented in table format, according to the MedDRA system organ classification. The system organ class (SOC) and Preferred Term should be used. Exceptionally, the Lowest Term Level or High Level Terms may be justified. As a general rule, any adverse events should be assigned to the most relevant SOC in relation to the target organ (for example, PT ‘Liver function test abnormal’ should be assigned to the SOC ‘Hepatobiliary disorders’ rather than to the SOC ‘Investigations’).

The summary table can be the same as in eCTD Table 2.7.4.3. Data should be pooled across studies where possible and appropriate comparisons with placebo or comparator arms provided, if available.

Subsections should be presented as follows:

* Common AEs
* AEs by severity
* AEs by relationship to study drug

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of the safety data.*

*<Text>*

* 1. Adverse drug reactions

This section should focus on the events where, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, on findings from non-clinical or epidemiological studies, and/or on causality assessment from individual case reports. Reversibility of the event should be addressed as appropriate. A table format should be used with a brief explanation as to why each event is being classified as ADR.

<Text>

This table is to be reflected in the ADR table from section 4.8 of the SmPC. The methodology used for defining ADRs and the database used to calculate ADR frequency should be described.

<Text>

**ADR table proposed for inclusion in the SmPC**

|  |
| --- |
| <System Organ Class> |
| Very Common | <PT (%\*)><PT (%)><PT (%)> |
| Common | <PT (%\*)><PT (%)><PT (%)> |
| Uncommon | <PT (%\*)><PT (%)><PT (%)> |
| Rare | <PT (%\*)><PT (%)><PT (%)> |
| Not known |  |
| <System Organ Class> |
| Very Common | <PT (%\*)><PT (%)><PT (%)> |
| Common | <PT (%\*)><PT (%)><PT (%)> |
| Uncommon | <PT (%\*)><PT (%)><PT (%)> |
| Rare | <PT (%\*)><PT (%)><PT (%)> |
| Not known |  |

\* Actual frequency calculated in the database described

***Assessor’s comment***

*Comment on the justification of the ADR list and whether it is appropriately reflected in the product labelling.*

*Is the safety profile in accordance with that expected from non-clinical studies and known class effects?*

*Are some patients particularly at risk? Are there specific risk factors for the occurrence of ADRs (dose, duration of exposure, co-morbidity etc.)? Are any preventive measures mentioned in the SmPC (warning on risk factor, monitoring, etc…)?*

*<Text>*

* 1. AEs of special interest, serious adverse events and deaths, other significant events

Provide the list of AEs of special interest (AESI) with the justification of their selection.

Present summary tables of AESIs, serious AEs (SAE) and deaths. Results should be presented by SOC and PT, including data on severity of SAEs.

If any, present summary tables of AESIs, SAEs and deaths considered related to the product with a brief explanation as to why each event is being classified as ADR/causally related.

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of these AEs and ADRs,* *and whether they are appropriately reflected in the proposed product labelling.*

*<Text>*

* 1. Discontinuation and dose modification due to adverse events

Discontinuations of treatment and discontinuations of study due to AE should be presented in separate tables. Discontinuations of treatment due to ADR/SADR should also be clearly summarised; it should be specified whether they were temporary or permanent. Dose reductions, dose interruptions/delays should also be described in this section.

Note that discontinuations (of treatment or study) for reasons not associated to AEs should be presented in the participant flow and not repeated in this section.

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of ADRs leading to treatment or study discontinuation. Is there any pattern of discontinuations that is concerning? Is the proportion of patients with dose reductions/delays acceptable? Does the proportion of study discontinuations due to AEs/ADRs impact on the validity/interpretability of the results*

*<Text>*

* 1. Safety in special populations

Include as many subsections as relevant and present data in summary tables.

Summarise briefly all available information used to substantiate specific statements on special populations in the product information, including elderly, paediatric population, pregnant women, patients with hepatic or renal impairment, genetic polymorphism, …

Complete the overview AE table below, which can be adapted to other special populations, as relevant.

**Overview of AEs by age (adults)**

|  | Study drug | Comparator |
| --- | --- | --- |
| Age (y) | <65n (%) | 65-74n (%) | 75-84n (%) | 85+n (%) | <65n (%) | 65-74n (%) | 75-84n (%) | 85+n (%) |
| Total AEs |   |   |   |   |  |  |  |  |
| Total SAEs |   |   |   |   |  |  |  |  |
| Fatal SAEs |   |   |   |   |  |  |  |  |
|  |
| Total ADRs |   |   |   |   |  |  |  |  |
| Total SADRs |   |   |   |   |  |  |  |  |
| Fatal SADRs |   |   |   |   |  |  |  |  |
|   |
| AEs leading to treatment discontinuation |   |   |   |   |  |  |  |  |
| ADRs leading to treatment discontinuation |  |  |  |  |  |  |  |  |
|   |
| <Relevant AEs> |   |   |   |   |  |  |  |  |
| <Relevant AEs> |   |   |   |   |  |  |  |  |
| <Relevant AEs> |   |   |   |   |  |  |  |  |
|  |
| <Relevant ADRs> |   |   |   |   |  |  |  |  |
| <Relevant ADRs> |   |   |   |   |  |  |  |  |
| <Relevant ADRs> |   |   |   |   |  |  |  |  |

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of AEs and ADRs in special populations and whether they are appropriately reflected in the proposed product labelling.*

*<Text>*

* 1. Safety related to drug-drug interaction and other interactions

Provide a brief summary of pharmacokinetic and pharmacodynamic interactions directly relevant for safety. Relevant safety experience from clinical data on other concomitant medication use should also be considered.

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of interaction safety data and whether they are appropriately reflected in the proposed product labelling. Are the most frequent medications typically administered to the target population addressed?*

*<Text>*

* 1. Laboratory and other findings

Provide a brief summary of the most important information on laboratory abnormalities related to AEs. If relevant, any finding related to vital signs, physical examinations (e.g. weight loss) should be mentioned in this section.

<Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of laboratory data and whether they are appropriately reflected in the proposed product labelling.*

*<Text>*

* 1. Post marketing experience

Provide information from post marketing experience, if any available.

<N/A> <Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of information from post marketing experience and whether it is appropriately reflected in the proposed product labelling.*

*<Text>*

* 1. In vitro biomarker test for patient selection for safety

If in vitro testing was used to exclude subjects based on safety concerns, provide the scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).

Describe the analytical method including assay platform, specimens, and read-out method. Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or by concordance with a clinically valid reference assay. Cut-point selection should be described in detail since it is of particular importance for the benefit/risk assessment.

<N/A> <Text>

***Assessor’s comment***

*Comment on the strength of evidence and relevance of information about the proposed biomarker. Is there sufficient justification for the use of the biomarker to select patients based on safety? Is the proposed product labelling sufficiently clear in this regard?*

*<Text>*

* 1. Overall assessment of clinical safety
		1. Discussion

*This should include a brief summary of the key safety findings and a critical discussion focusing on the strengths and weaknesses of the whole safety package submitted to inform the benefit/risk assessment of the product.*

*It is based on the boxed comments of the Clinical Safety section but should not be a copy/paste of all these comments. This discussion should emphasise the main areas of uncertainty that should be addressed by the Applicant in response to the LOQ.*

*In terms of structure, it should follow the sections of the results above. Include a discussion on the fulfilment of requirements (legal, guidelines, scientific advice) and on the key findings and deficiencies, which should be part of the B/R assessment.*

*Comment on what safety findings should be considered for inclusion in the safety specification of the RMP.*

<Text>

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

*Describe the data missing from Module 5, why they are missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. what data are required.*

[*https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice#guidance-for-great-britain-conditional-marketing-authorisation-applications*](https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice#guidance-for-great-britain-conditional-marketing-authorisation-applications)

*The following statement should be used:*

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

<Text>

* + 1. Product information

This should be a general assessment of the suitability of the proposed SmPC. Comments and edits should be made directly in the attached product information.

Ensure that all information in the safety sections of the SmPC is explicitly supported by the scientific assessment.

<Text>

* + 1. Conclusions

This should be a general statement on the quality and relevance of the Clinical Safety documentation. It should conclude whether an MO is raised (and on what ground) or only OCs and whether additional studies are required.

<Text>

1. Benefit risk assessment

The B/R should be summarised in the following table

**Summary of benefit and risk**

|  |  |  |
| --- | --- | --- |
| Decision factor | Evidence | Uncertainties |
| Analysis of condition | *Key aspects of the disease/condition studied that are important for the B/R assessment**Aims of treatment* |  |
| Current treatment options and unmet medical need | *Main treatments available**Unmet medical need* |  |
| Benefit | *Outcomes related to favourable effects* | *Important limitations about knowledge of favourable effects**Or:*<There are no remaining uncertainties that have an impact on the B/R> |
| Risk | *Outcomes related to key unfavourable effects (including loss of efficacy, interactions, potential for abuse, ….)* | *Important limitations about knowledge of unfavourable effects**Or:*<There are no remaining uncertainties that have an impact on the B/R> |
| Risk management |  |  |
| Conclusion | B/R <positive> <negative> | *Explain reasons (value judgments of benefit and risk)* |
| Recommended indication |  |  |
| Recommended option for MA | <full> conditional> <under exceptional circumstances> | *Explain reasons* |

1. Assessment of request of conversion of conditional MA to full MA
2. Assessment of request of additional market protection
3. List of post-authorisation measures and recommendations
	1. Specific obligations for Conditional Marketing Authorisation and Marketing Authorisation under exceptional circumstances

| **Specific obligation** | **Description** | **Due date** |
| --- | --- | --- |
| **SOB 1** |  |  |
| **SOB 2** |  |  |
| **SOB 3** |  |  |

* 1. Mandatory post-authorisation measures that are part of the marketing authorisation

| **Post-authorisation measure(s)** | **Reason** | **Due date** |
| --- | --- | --- |
| **Post-authorisation measure 1**Classification: …. |  |  |
| **Post-authorisation measure 2**Classification: …. |  |  |
| **Post-authorisation measure 3**Classification: …. |  |  |

\* Classification:

category 1 = PASS or other studies (including PAES)

category 3 = all other studies (e.g. additional pharmacovigilance activities) reflected only in the RMP

* 1. Recommendations (not mandatory)

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

1. Product information attachments
	1. Annotated SmPC
	2. Annotated PIL
	3. User consultation

The User Testing evaluation questionnaire should be appended.

Alternatively, if relevant, the following statement should be used:

<A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.>

1. LIST OF QUESTIONS RFI 1

**Major objections**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance**

**Other concerns**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance**

1. ASSESSMENT OF RESPONSES TO RFI 1

Responses should be completed by the Applicant and assessed in the Response document template (<https://www.gov.uk/government/publications/response-template-for-applicants>).

<Refer to separate Assessment Report of Responses>

<Following the review of the responses <no> <MO> and /or <OC> remain(s).

*If there was an MO assessed in the responses insert below an updated table Summary of benefit and risk.*

1. LIST OF QUESTIONS RFI 2

*Copy here the list of questions from the Assessment Report of Responses.*

**Major objections**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance**

**Other concerns**

**Pharmacokinetics**

**Pharmacodynamics**

**Efficacy**

**Safety**

**Pharmacovigilance**

1. ASSESSMENT OF RESPONSES TO RFI 2

Responses should be completed by the Applicant and assessed in the Response document template (<https://www.gov.uk/government/publications/response-template-for-applicants>).

<Refer to separate Assessment Report of Responses>

<Following the review of the responses <no> <MO> and /or <OC> remain(s).

*If there was an MO assessed in the responses insert below an updated table Summary of benefit and risk.*