EMA/257294/2024

Human Medicines Division

Version 2

Scientific document

For paediatric investigation plan or product-specific waiver

<Active substance(s)>

<Case number> - Include case number before uploading this document (e.g. *EMA/PE/0000123456)*

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Do not amend the style of the template; keep existing fonts and headings when completing

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* Indentation: 0
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Inserting tables: Please use plain table and where possible in portrait layout.

Inserting pictures and figures: Keep the document flowing.

Do not use section breaks (unless your table can not fit in portrait layout).

Do not use links, fields, and citations; keep the document free of footnotes and endnotes.

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1. Application summary

This application is submitted to meet the paediatric requirements under Regulation (EC) No 1901/2006 as amended.

*Applicants are advised to ensure that all information in IRIS is accurate and complete, as the application summary will be automatically generated and included in the summary report.*

|  |
| --- |
| **Text boxes with borders in this document are for EMA use only, do not delete or insert text in these.** |

Comments

|  |
| --- |
| **EMA Scientific Officer:**Assessment of the timing of the application: <Template text below><As specified in the EMA Procedural advice on paediatric applications EMA/672643/2017, according to Article 16 of the Paediatric Regulation, applications for agreement on a waiver or a PIP should be submitted, unless duly justified, “not later than upon completion of the human pharmacokinetic (PK) studies”, as specified in Section 5.2.3 of Part 1 of Annex 1 of Directive 2001/83/EC'. Recital 10 of the Regulation states that “paediatric investigation plans should be submitted early during product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing-authorisation applications are submitted.”><EMA procedural advice published on the EMA website states that “the timing of submission should not be later than the end of healthy subject or patient PK which can coincide with the initial tolerability studies, or the initiation of the adult phase-II studies (proof-of-concept studies); it cannot be after initiation of pivotal trials or confirmatory (phase-III) trials. Applicants are welcome to submit their PIP applications during or even before initial PK studies in adults. However, submitting a first application for a new active substance during confirmatory or phase-III trials in adults, or after starting clinical trials in children, is likely to be considered “unjustified”.>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

1. Overview of the disease(s), condition and pharmacological rationale
	1. Pharmacology and mechanism of action

Only a high-level summary is expected in this section, focusing on the mode of action and proof of concept supporting the proposed paediatric development.

Any clinical or other relevant data already available at the time of PIP submission, including description of planned adult development and existing evidence, should be provided in section 4.

If applicable and necessary, this section should also include information on ontogeny, particularly where absorption, distribution, metabolism and excretion (ADME) pathways involved in the medicine’s disposition are still maturing in the target population. Such developmental considerations may justify differences in efficacy and/or safety between adults and children, and appropriate justification should be provided.)

Please indicate whether data on exposure-response relationship are available in adults and children or whether generation of such data is planned.

Describe the nature of the relationship (e.g. is the exposure/response or pharmacokinetic/pharmacodynamic (PK/PD) relationship investigated or defined), and whether any covariates such as age, body weight or body surface area, have been identified.

Where relevant, include known maturation-related or developmental factors that may influence exposure or response in specific and relevant age subsets (e.g. age-related differences in immunoglobulin levels, or receptor expression).

Indicate whether the therapeutic window of the medicinal product is considered wide or narrow, and provide justification where appropriate.

Specify whether pharmacodynamic (PD) parameters or biomarkers have been identified in relation to the drug’s mode of action in the intended paediatric population?

<Text>

* 1. Summary of differences/similarities in the condition between populations (e.g. adult vs paediatric)

The proposed condition(s) should be described and discussed in the context of current medical practice taking into account the medicinal product’s mechanism of action, identified paediatric therapeutic needs and its potential use in the target population. Where appropriate, the Medical Dictionary for Regulatory Activities (MedDRA)classification system should be used as a guiding framework, particularly when referring to terminology or structuring the condition(s). Relevant orphan medicine designation(s) should also be referenced, where applicable. Unless the development only concerns children, starting point usually is the indication(s) being developed or already authorised for use in the adult population.

Clear information must be provided on the paediatric age range subset(s) affected by the disease/condition. This should include a description of the incidence or prevalence of the condition across the relevant paediatric age groups, supported by appropriate databases or other scientific sources.

If the condition does not occur in certain paediatric subsets, this must be substantiated with evidence further discussed in section 3 under the grounds for waiver.

Where extrapolation is proposed, this section should outline the basis of the extrapolation concept. Reference is made to the published guidance: Committee for Medicinal Products for Human Use(CHMP) Structured guidance on the use of extrapolation EMA/CHMP/13622/2022: <https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_en.pdf>, which should be completed and included in the relevant sections below. For additional guidance, see also Q&A 1.7 on the EMA website, “How do I discuss the use of extrapolation in my PIP submission?” <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/paediatric-medicines-research-development/paediatric-investigation-plans/paediatric-investigation-plans-questions-answers#1-paediatric-procedures-and-applications-67499>

<Text>

* 1. Current methods of diagnosis, prevention, or treatment in paediatric populations

Provide a high-level discussion of existing strategies for the diagnosis, prevention, or treatment of the targeted disorder, depending on the proposed condition for this application, which are currently available in the European Union (EU). This should include unauthorised treatment methods if they represent the standard of care (e.g. as referenced in internationally-recognised treatment guidelines).

Please contextualise the discussion, as applicable, including the accompanying tables, with reference to available treatment guideline(s) and recommendations.

The list of available treatments, including those authorised by the national authorities or via the centralised procedure should be included in the table below.

The invented name and the approved use of any medical devices marketed in the EU should be provided, if applicable.

This section is intended to support and inform the discussion in section 2.4. Please avoid duplication of content already presented in sections 2.3 and 2.4, cross-referencing is sufficient.

**Use this table for non-authorised or off-label products in the proposed condition.**

Non- authorised or off-label medicinal products in the proposed condition

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Active substance or INN** | **Indication and age groups** | **Product used off-label** (e.g. for indication, age, dosage, formulation) | **Product not authorised** | **Source of recommendation (e.g.: treatment guideline)** |
|  |  |  |  |  |
|  |  |  |  |  |

**Use this table for authorised medicinal products in the proposed condition.**

Authorised medicinal products in the proposed condition

|  |  |  |
| --- | --- | --- |
| **Invented name and active substance or INN** | **Indication and age groups** | **Type of authorisation (e.g. centralised, national, mutual recognition)** |
|  |  |  |
|  |  |  |

<Text>

* 1. Description of the fulfilment of therapeutic needs and/or significant therapeutic benefit

**Related to therapeutic needs**

Acknowledging all currently available products as referenced in the tables above, please indicate whether they are authorised for the intended target indication and specify the paediatric age ranges for which they are authorised. If not authorised, clarify whether their use is evidence-based e.g. if they are recommended in relevant treatment guidelines.

Identify any current limitations in the use of the available products, including their use in specific paediatric age groups.

*Additionally indicate whether there is any need for a specific age-appropriate pharmaceutical form or route of administration.*

<Text>

**Related to significant therapeutic benefit**

Based on the identification of a target population with existing unmet medical needs above, please describe how the proposed product is expected to contribute to a potential significant therapeutic benefit in addressing currently **uncovered** preventative, therapeutic, or diagnostic needs within the proposed target indication; specify the relevant paediatric age ranges.

The following aspects should be considered, where applicable, when outlining the significant therapeutic benefit of the product. This should be based on current knowledge, taking into account the mechanism of action, potential toxicities or harms and pharmacodynamic (drug) interactions, leading to:

* A reasonable expectation of safety and efficacy in treating a paediatric condition where no authorised paediatric medicinal product is on the market;
* expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned;
* expected improvement in safety in terms of reduced adverse events or minimised potential medication errors;
* an improved dosing scheme or method of administration that enhances safety, efficacy or patient compliance;
* availability of a new clinically relevant age-appropriate formulation;
* availability of new and clinically relevant therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population. This may include addressing specific needs or subsets within the population;
* an improved expected benefit-risk balance compared to existing treatments that may be unsatisfactory, highlighting the need for alternative therapeutic approaches;
* an expected clinically relevant advantage or a major contribution to patient care based on either of the above points;
* an expected improvement in the quality of life of the child.

<Text>

* 1. Proposed indication(s) in relation to the proposed condition and selected paediatric subsets

Based on the considerations outlined above, a conclusion should be drawn regarding the most appropriate target indication and paediatric age subset(s) for which the product, under the proposed condition, is expected to provide a significant therapeutic benefit and/or address an unmet therapeutic medical need. Cross-reference to relevant sections of this template as appropriate.

Within the defined PIP condition the product may be developed in one or more specific indications, depending on the selected paediatric subgroups. The scientific rationale for the proposed indication(s) and subgroup(s) should be clearly discussed. This represents the proposed indication in the paediatric population for the purpose of a PIP, and at the time of submission of the PIP, within a specific condition. For example, within the broader condition of “treatment of asthma,” the proposed indication might be “treatment of acute asthma episodes in children from 6 to less than 18 years of age.”

Where applicable, refer to specific regulatory or scientific guideline(s) and discuss their relevance to paediatric development, including any recommendations that support the proposed approach.

It is important to note, that the Regulation does not require the PIP to be limited to the proposed wording of the adult indication, however, a scientific relationship between adult and paediatric development is generally expected. This obviously does not apply to paediatric only developments or when development is initiated first in children.

In addition to chronological age, the selection of paediatric participants may also be based on other variables, such as gestational age, pubertal stages and gender, either independently or in combination with age, where scientifically justified.

<Text>

* 1. Summary of regulatory advice

This section should align with, and expand upon the information provided in the IRIS submission table.

If any regulatory advice or feedback documents have been received, they should be annexed to the submission. A very high-level summary of the key outcomes should be included here, specifying the type of advice received and its source (e.g. quality, non-clinical, clinical from CHMP, SAWP, NCAs, international regulators).

In addition please summarise the main points of the advice that are relevant to the proposed paediatric development. In cases where there is divergence from the advice received, provide a summary of the relevant points and include a justification for the alternative proposal.

<Text>

* 1. Feedback received from networks, experts and patient groups

If applicable, describe how paediatric networks and/or experts have been approached; summarise the feedback received and annex any relevant documentation.

Explain involvement of patients, caregivers and their organisations including any involvement of young people. Summarise the feedback received and annex supporting materials where available.

This section may also include a discussion on the feasibility of performing clinical trials in the target paediatric indication. If feasibility is limited, this may support a waiver request – cross-reference to relevant sections as necessary.

<Text>

Comments

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| **EMA Scientific Officer:**Comment on justifications related to the use of extrapolation as appropriate: this forms the basis for accepting extrapolation as part of the extrapolation concept = which leads to describing what identified uncertainties remain, to be addressed in the extrapolation plan (see 4.3.2)<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

1. Application for waiver(s)

This section applies to either product-specific waiver applications covering all paediatric subsets (full waiver), or to waiver applications covering a paediatric sub-population, alongside a proposed PIP (partial waiver).

* If this application is for a **full waiver**, then sections 4 and 5 of this template are **not** applicable. In this case indicate “Not applicable” for this entire section, and remove the subheadings accordingly.

<Not applicable>

* 1. Overview

This section should summarise the grounds for the requested waiver, whether it applies to the entire paediatric population (full waiver) or to specific sub-populations (partial waiver).

If a paediatric sub-population is proposed to be excluded, reference should be made to section 2, including a discussion on:

* The availability of other medicinal products, or
* The existence of an established standard of care that addresses the treatment needs of the excluded paediatric group.

The justification for waiving the obligation to study the paediatric population (either as a whole or in part) must be based on scientific principles and evidence including:

* The pharmacological properties and mechanism of action of the product;
* the clinical characteristics of the target condition and its epidemiology;
* the identified therapeutic need;
* the availability of licensed treatments.

Reference may be made to the discussion in section 2.

The following considerations should be reflected in the general discussion:

* Why is the medicinal product not expected to be useful in paediatrics or in a paediatric subpopulation for the proposed condition?
* What evidence supports the claim that no identifiable paediatric (sub-) population exists in which a positive benefit-risk balance can be meaningfully demonstrated?
* What additional scientific information would be required to enable further development of this product in paediatrics.
* Are there access limitations to certain paediatric subpopulation(s) (e.g. infants below a body weight of 6 kg for stem-cell harvesting).
* Are there developmental/maturation related or physiological factors specific to the paediatric (sub-)population (e.g. sexual development, maturation of the immune or coagulation system) that would support the waiver request?

The justification for waiving paediatric studies/development should be supported by scientific and clinical research-based evidence, recognising that this may evolve over time as more evidence emerges during product development.

Each paediatric sub-population for which a waiver is requested must be justified individually, using the appropriate grounds as defined in Article 11 of Regulation (EC) No 1906/2006. Waiver grounds may differ across paediatric subsets and should be selected based on the specific characteristics and needs of each group.

To identify the most appropriate waiver grounds, each should be examined consecutively and hierarchically taking into account the therapeutic need, where relevant.

<Text>

* 1. Ground 1: the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s)

This waiver ground applies when the condition or disease does not exist in the paediatric population (this includes diseases or conditions for which no cases or only very few paediatric cases have been reported, and which occur only or predominantly in adults such as breast cancer or lung cancer.

<Text>

<Not applicable>

* 1. Ground 2: the specific medicinal product does not represent a significant therapeutic benefit

This waiver ground applies when the condition exists in the paediatric population, but there is no identified therapeutic need which may occur when no therapy is required, or when existing therapies are considered adequate, and the proposed product is not expected to offer additional benefit.

In such cases, evidence should be provided to demonstrate the availability and adequacy of existing therapies applicable to the paediatric population.

Where relevant, and with cross-reference to section 2, the applicant should discuss the rarity of the condition and the epidemiological paucity for the target paediatric population. In addition, the ability and/or feasibility to conduct meaningful clinical trials or development should be addressed. It should be clearly demonstrated that conducting paediatric trials would be unnecessary or unjustified, particularly if such trials in the paediatric population are not likely to generate any evidence to support a future marketing authorisation application.

<Text>

<Not applicable>

* 1. Ground 3: the specific medicinal product is likely to be ineffective or unsafe

This waiver ground applies when the condition and disease exists in the paediatric population and an unmet need is recognised, yet development is not considered warranted since, based on the pharmacological properties of the medicinal product, it is not expected to be effective and/or safe in the paediatric population relative to the identified unmet need.

In such cases the applicant should provide a scientific justification outlining the pharmacologic rationale for the anticipated lack of efficacy and/or safety. This may include, for example, absence of relevant receptors, differences in disease pathophysiology, or known class-related safety concerns. The justification should be supported by available non-clinical or clinical data.

Where evidence suggests a potential safety concern in the paediatric population, the applicant should discuss whether further research may be applicable to investigate the potential important safety issue. This may include additional animal studies or further research in adult populations. The applicant should also consider whether a deferral, may be more appropriate than a waiver, particularly in cases where the safety concern is not yet substantiated. In addition, it should be discussed how the safety concern could be monitored or mitigated.

In addition, the applicant should assess the likelihood of ineffectiveness of the medicinal product in the target paediatric population and provide a clear rationale for lack of expected efficacy. This should be based on mechanistic understanding and supported by relevant evidence. It should be demonstrated that paediatric development would be unnecessary or unjustified, especially if such development is unlikely to generate data that would support a future marketing authorisation application.

<Text>

<Not applicable>

* 1. Conclusion

After a discussion of the various potential waiver grounds, the applicant should propose the most appropriate ground for the waiver for each paediatric subgroup as applicable, respecting the established hierarchy: ground 1 should be considered first, followed by ground 2, and finally ground 3. Only one of the three grounds, the most relevant and scientifically substantiated, should be proposed for each paediatric subgroup.

<Text>

Comments

|  |
| --- |
| **EMA Scientific Officer:**The selected paediatric age groups are <not> considered adequate.The proposed grounds are <not> considered adequate.<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

1. Proposed paediatric investigation plan

This section is not applicable for product-specific waiver applications for all paediatric subsets (“full waiver”); please indicate “Not applicable” here and delete the subheadings.

<Not applicable>

* 1. Quality aspects
		1. Existing pharmaceutical forms

Please provide a brief overview of the existing formulations with particular attention to their relevance for the paediatric population or subsets. Discuss the suitability of the existing formulations for each relevant subset of the paediatric population, taking into account factors such as age-appropriateness, dosage form, route of administration, and excipient safety.

<Text>

* + 1. Proposed pharmaceutical forms for paediatric use

The rationale for the proposed quality study/ies including the key elements, should be clearly outlined. This should be justified in context of intended age group(s) focusing on the youngest age group(s).

Applicants should discuss the advantages and disadvantages of the proposed pharmaceutical form and route of administration in the context of the following aspects:

* the condition(s) to be treated and expected treatment duration;
* the physicochemical and biopharmaceutical properties of the active substance;
* the necessity and safety of specific excipients;
* the need for and suitability of measuring and administration devices;
* stability considerations;
* dosage requirements and the risk of dosing errors;
* user-related factors such as ease of administration and patient/caregiver acceptability.

(Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2: https://www.ema.europa.eu/en/pharmaceutical-development-medicines-paediatric-use-scientific-guideline)

In particular the following points need to be considered. Some sections, however, may need to be updated before clinical studies are initiated in paediatric patients. If such information is not yet available, any gaps in knowledge should be clearly highlighted.

* Discuss the need (or not)for development of a paediatric formulation. If existing formulations are considered adequate, this should be justified in relation to the target paediatric subsets, estimated dose ranges, and the need for dose flexibility (e.g. weight-tiered, mg/kg, or mg/m²).
* Address the intent to use interim formulations and the associated risks, particularly if these involve modifications of adult formulations. (see points of discussion below for alternative administration strategies).
* Clearly justify the proposed overall pharmaceutical development strategy and discuss all considered options. If a specific paediatric-appropriate formulation is deemed unfeasible, supporting data (e.g. physico-chemical, ADME (absorption, distribution, metabolism, excretion), pharmaceutical, biopharmaceutical, pre-clinical, or early clinical) should be provided demonstrating the limitations or constraints.
* Consider the need for a specific formulation for neonates Including administration-specific aspects such as the use of dextrose solution as solvent of dilution instead of sodium chloride solution to prevent hypernatraemia potentially caused by “flushing” with physiological sodium chloride solution (Guideline on the investigation of medicinal products in the term and pre-term neonate EMEA/536810/2008)).
* If applicable, discuss alternative administration strategies (e.g. for those children unable to swallow an oral solid preparation) and justify their need and feasibility and dose accuracy (e.g. dispersing, crushing or subdivision of tablets, opening of capsules, mixing or co-administration with food).
* Discuss whether acceptability (including palatability) should be assessed in paediatric clinical studies with the target paediatric population and caregivers.
* If administration with food is foreseen:
	+ provide a risk assessment of potential effects on bioavailability, based on pharmaceutical and biopharmaceutical properties,
	+ provide or propose key elements for compatibility studies with food and/or drink.
* If relevant, discuss the need for administration through feeding tubes. Where this is used, either as a main route or as a very likely option, the feasibility and appropriateness of administration through the tube needs to be addressed.
* If available, discuss additional safety data that is/will be available from pre-clinical studies and safety measures, and clinical data to be gathered from paediatric studies.
* If already available, justify the choice of primary packaging(s) selected, including the packaging size in view of the posology, and discuss any possible risk of overdosing.
* Discuss if any dosing/administration device is needed and its suitability for the proposed age groups. Consider that accuracy of measuring devices for paediatric medicines with a steep dose/pharmacodynamic response curve or narrow therapeutic window may require special considerations. For other devices, the ease of administration by the child or its caregiver, difficulties in administration to unwilling children, and the robustness of the device in daily practice should be considered.
* Confirm that the guidelines were followed or justify deviation:
	+ Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2: <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf>

and

* + Reflection paper: formulations of choice for the paediatric population EMEA/CHMP/PEG/194810/2005: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population\_en.pdf

<Text>

* + 1. Justification of qualitative and quantitative composition

Discuss and justify the necessity of each excipient and quantity used in the paediatric formulation, in particular for new excipients and those with potential (dose-related) local or systemic pharmacological effects. Based on estimated doses, justify safety of each excipient in relation to maximum daily exposure (mg/kg), target age group, route of administration and duration of treatment (see EMA website on Paediatric formulations: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/paediatric-medicines-research-and-development/paediatric-investigation-plans/paediatric-formulations). When there is no or insufficient evidence in a particular age group, the rationale for extrapolation from other age groups and associated risk should be discussed.

If this information is not yet available, please discuss how and when it is planned to be agreed with the PDCO.

Ensure that quality aspects provided in the key elements are justified here.

<Text>

Comments

|  |
| --- |
| **EMA Scientific Officer:**EMA will insert proposed quality key elements above comments for discussion if necessary<The proposed formulation(s) are <not> considered adequate to cover the selected age groups.><Discussion maybe considered with PFOEG.><Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text>**Questions for Paediatric Formulation Operational Expert Group (PFOEG):**<N/A><Text> |

* 1. Non-clinical aspects
		1. Existing non-clinical data

Mechanism of action

This should be brief: data summarised below is needed to support paediatric development and justify the key elements for the various studies. It should duplicate the Investigator’s Brochure (IB).

Provide a concise overview of the pharmacological rationale and relevant proof of concept data (in vitro, in vivo) to support the use of the compound in the intended paediatric population. Cross-refer to section 2.1 as needed.

To also be addressed, if relevant:

* Species differences in pharmacodynamicactivity.
* Paediatric-specific pathophysiology.
* Potential for off-target effects.

Clarify whether the compound is first-in-class, and discuss similarities or differences compared to other compounds in the same class.

If there is any concern of effects on growth and/or maturation please summarise:

* Age-related differences in pharmacodynamic activity, such as available information on the ontogeny of expression and function of the targeted receptor(s), enzyme(s), or pathway(s), particularly where differences are expected and such data is available.
* Potential for on- or off-target activity in organs undergoing significant development in part of or all of the target population.

<Text>

Safety pharmacology

Please summarise:

* Organ systems evaluated, also if safety pharmacology endpoints were included in the repeat-dose toxicity studies.
* Adverse findings, if any, with exposure margins over clinical anticipated exposure.

<Text>

Pharmacokinetics (PK)

Please summarise:

* CYP involvement, non-clinical species relevance in terms of metabolism,
* Distribution including potential to distribute to the brain,
* Substrate for drug transporters?
* Major elimination route
* Significant species and/or sex differences in pharmacokinetic parameters, if any.

<Text>

Repeat-dose toxicity studies

Please describe species, duration, route, regimen, age of the animals at study start, target organs for toxicity, and reversibility of effect.

Discuss the clinical relevance of the observed adverse findings including exposure margins over clinical anticipated exposure and if available, findings confirmed in clinical studies thus far should be included here.

Discuss potential underlying mechanism for unexpected findings.

<Text>

<Not available>

Reproduction

Describe outcome of embryo-foetal development (EFD), fertility and early embryonic development (FEED) and (enhanced) pre- and postnatal ((e)PPND) study(ies) including endpoints assessed in the offspring and pup exposure, if available.

Describe outcome of juvenile animal toxicity studies (JAS), if such study(ies) are already conducted. This should include the species, route, regimen, age range of the animals, endpoints. Discuss whether the study identified novel and/or enhanced toxicities, their reversibility, clinical relevance and exposure multiples over clinical anticipated exposure. Discuss whether significant age-related differences in systemic exposure were observed compared to adult animals treated with a similar dose.

Describe planned monitoring for adverse findings, where relevant.

<Text>

<Not available>

Genotoxicity

Describe outcome of the standard non-clinical safety pharmacology battery, if relevant.

<Text>

<Not available>

Carcinogenicity

Please list any study conducted and main findings, if available.

<Text>

<Not available>

Other

e.g. mechanistic studies as follow-up to certain findings in studies described above, tissue-cross reactivity studies, published data on viability, development, fertility of relevant knock-out animals.

<Text>

<Not applicable>

* + 1. Proposed non-clinical development

Describe the proposed non-clinical strategy to support paediatric use in addition to classical non-clinical development.

<Text>

* + 1. Justification of overall strategy and juvenile safety studies
* Weight-of-evidence discussion of the need for additional non-clinical safety investigations including JAS (refer to ICH S11 guideline). For anti-cancer products, refer to the EMA/FDA Common Commentary concerning paediatric oncology development plans, if available.
* If studies in juvenile animals are proposed in the key elements, justify the selected species and study design taking into account the youngest intended patient age and developmental periods of organ system(s) of toxicological concern (refer to ICH S11 guideline).
* Discuss the need for additional non-clinical proof of concept data. Indicate whether animal models exist and whether they are appropriate to evaluate the effect of the product and to extrapolate the results to humans.
* Discuss the prerequisites for human administration with particular attention to paediatric use.
* Justify all key elements proposed in the IRIS portal webform, focusing on species, route, regimen, age of the animals at study start, dosing period, endpoints, reversibility, and toxicokinetics (TK). Generally, each juvenile animal study should include the core endpoints defined in ICH S11. Each additional endpoint should be justified to address an identified safety concern.

Comments

|  |
| --- |
| **EMA Scientific Officer:***EMA will insert the proposed non-clinical key elements above comments for discussion if necessary*<Text><The proposed non-clinical development is <not> considered adequate to cover the selected age groups.> <It should be discussed whether the proposed non-clinical development is considered adequate to cover the selected age groups.><Discussion maybe considered with NcWP.>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text>**Questions for Non-clinical Working Party (NcWP):**<N/A><Text> |

* 1. Clinical aspects
		1. Existing clinical data and planned studies in adults

Discussion of the overall strategy for clinical development should be brief. The data summarised below should support development and must not duplicate the Investigator’s Brochure (IB). Please indicate planned studies in adults that could produce data relevant to paediatric development.

Please focus on what data have demonstrated so far, and what confirmatory data are expected.

<Text>

Pharmacokinetic properties

Please provide a summary of ADME (absorption, distribution, metabolism, excretion) and toxicity data with emphasis on any implications for the pharmacological or dosing strategy in children.

Describe the main available pharmacokinetic parameters:

Linearity of the kinetics, Tmax, Cmax, absolute bio-availability, volume of distribution, plasma clearance, half-lives (T½, terminal T½); hepatic extraction ratio for medicinal products primarily eliminated through the liver (comparison of plasma clearance to normal liver blood flow).

If extrapolation of efficacy data is planned, list the available PK and PD data, or in which studies further data will be generated.

<Text>

Pharmacodynamic properties

*Describe available data on pharmacodynamic (PD) parameters, including clinical data and biomarkers. Indicate whether PD data are available in animals and/or adults and whether they relate to the effect of interest and other pharmacological effects. Discuss, how maturation may influence the PK-PD relationship. If available, provide data on the age at which 90-100% of adult maximum PD response as a function of plasma concentration is reached.*

<Text>

Interaction with other medicinal products

Although the PIP is not intended to include all elements necessary for overall drug development, certain development requirements may need to be addressed here, specifically when they relate to paediatric-specific considerations.

<Text>

Summary of efficacy data

Provide a summary supporting efficacy and outcome measure used with emphasis on the total duration of exposure per patients and the total number of patients treated.

<Text>

<Not applicable>

Exposure-response analysis

Mention any performed or planned analysis and parameters used.

<Text>

<Not applicable>

Summary of safety data

Provide a summary identifying any safety signals, particularly serious AEs and reactions that could have a worse outcome in children or could be of concern (e.g. effects on growth, sexual maturity, neurobehavioral development). For the most common adverse events (AE) reported, discuss impact on the paediatric population, particularly where severity or clinical outcome may differ from adults.

<Text>

<Not applicable>

Comments

|  |
| --- |
| **EMA Scientific Officer:**<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

* + 1. Proposed clinical development

Summary of overall strategy and extrapolation plan

Provide a strategic overview of your paediatric development plan, linking:

* adult development (if related),
* existing evidence,
* unmet needs, and
* potential significant therapeutic benefit (cross-referencing sections 2 and 3; no specific or detailed information are expected here).

If extrapolation is involved, please follow the Structured guidance on extrapolation to present your extrapolation concept and plan, and include it separately with your submission (EMA/CHMP/13622/2022):

<https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_en.pdf>

This section should be used to reflect on identified challenges as regards the overall paediatric development strategy, related to any part you consider important to highlight.

This should include a conclusion on identified uncertainties as part of **extrapolation concept discussions** if applicable (as already reflected upon in sections 2.1 and 2.2 above), and **how these will be addressed as part of the extrapolation plan.**

<Text>

Graphic overview of milestones and timelines

A graphic representation of timelines, in relation to adult planned development, non-clinical data availability and pharmaceutical form development milestones, is requested. Please see the example below. If a graphic format is not possible, please provide the information in a table.

This should be consistent with section 5, which will report the initiation and conclusion dates of the studies part of the PIP.

Include timelines of the overall development plan, including the availability of formulations, completion of non-clinical studies, and other milestones that are conditional to the paediatric clinical development strategy. Please indicate any relevant adult study that would be used as a milestone for paediatric development.



* + 1. Strategy for paediatric dose selection and PK/PD evaluation
1. Summarise the high-level principles guiding the strategy for paediatric dose selection, e.g. matching PK exposure with adults, targeting similar PD responses, need for exposure response characterisation in children, based on pre-clinical evidence, etc.
2. The strategy for paediatric dose selection should be based on the expected differences in exposure response and disease progression between adults and children, considering pharmacology, real world data/evidence (RWD/E) and literature data. Please refer to the Committee for Medicinal Products for Human Use ICH guideline E11A on paediatric extrapolation EMA/CHMP/ICH/205218/2022 (https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline) Step 2b, Dose Selection.
3. <Text>

Modelling and simulation analyses supporting paediatric development

1. Describe the modelling and simulation (M&S) analyses proposed and role in the development.
2. Consult Modelling and simulation on the EMA website for any relevant update: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers.
3. If **modelling and simulation analyses are planned** as a substantial (or exclusive) part of the PIP, justification should be provided here for the proposed objective, data to be used and methodology. The relevant key elements should be entered in the IRIS portal webforms.
4. Provide all relevant model information which is available in adults and prediction at the time of PIP submission.
5. Relevant documentation for modelling and simulation (MIDD table of assessment, model analysis plan and model analysis report) should be provided, if available.
6. Where possible, in support of the analyses proposed include Table 1 from (Draft) [ICH M15 Guideline on general principles for model-informed drug development](https://www.ema.europa.eu/en/ich-m15-guideline-general-principles-model-informed-drug-development-step-2b-scientific-guideline) - Step 2b and successive version thereof as follows including at least MIDD planning stage:

|  |  |
| --- | --- |
| Item  | **Entry** |
| ***MIDD Planning Stage*** |
| Appropriateness of Proposed MIDD | 1. See instructions in [ICH M15](https://www.ema.europa.eu/en/ich-m15-guideline-general-principles-model-informed-drug-development-step-2b-scientific-guideline)
 |
| Technical Criteria |  |
| ***Key Assessment Elements*** |
| Question of Interest |  |
| Context of use |  |
| Model influence |  |
| Consequence of wrong decision |  |
| Model risk |  |
| Model impact |  |

1. The key elements form (KEF) should include clear objectives and high-level information regarding the M&S analysis and plan, detailed information and justification (e.g. objective of the model-based analysis, description of the current available model(s), description of the planned model analysis).
2. Clarify what the scope and role of M&S is in the development: describe, characterise, replace development.
3. Clarify proposed PK sampling and sampling volumes and how it will be done in the proposed study. It should be clear which studies will contribute to paediatric dose selection.
4. <Text>

Modelling and simulation analyses as part of the extrapolation plan

1. If extrapolation of efficacy is pursued through M&S, the methodology and how the analysis will be performed should be discussed here.
2. <Text>
3. <Not applicable>

Comments

|  |
| --- |
| EMA will insert the proposed modelling and simulation key elements above comments for discussion if necessary**EMA Scientific Officer:**1. **Scientific question of interest that M&S analysis are proposed to address:**

*Examples:* * M&S will be used to derive initial doses to be studied in paediatric trials from adult PK data.
* M&S will aid in study design
* M&S will be used to determine number of subjects, number of PK samples and sampling time points for participants in Study XYZ in the paediatric population from <age> to <age>…
* M&S will be used to support extrapolation of efficacy in the following (age) subgroups: <adolescents, children, toddlers, neonates>

<Text>1. **Type of model(s) analysis in the PIP:**

*Examples:* * The following analysis are proposed in the PIP: PopPK, PBPK, PK/PD, Exposure-response, QSP

<Text>1. **What type of data will be generated from the different paediatric age subgroup?**

*Examples:* * Adolescents RCT with PK/PD. Children from 6 to 12, single arm, PK only.
* Neonates, no clinical data – dose predicted based on M&S.

<Text>1. **Additional comments:**

<N/A><Text>**PDCO Rapporteur:**<Text>**PDCO Peer reviewer:**<Text>**Questions for Modelling and Simulation Operational Expert Group (MSOEG):**<N/A><Text> |

* + 1. Proposed clinical studies
1. **FOR EACH STUDY** included in the key elements form, please use the structure indicated below to detail justifications for the choice of - AT THE VERY LEAST - the key aspects indicated (cross-refer where applicable). All clinical studies, irrespective of the objectives (e.g. PK, PD, safety, efficacy), need to be included here. However, there is no need to repeat here the key elements table already provided in the submission.

Please justify, cross referencing to “Overall strategy”, the number of studies to be conducted, the paediatric subgroups to be enrolled in each of them and scientific rationale underpinning the chosen design (RCT vs single arm, etc), considering their interdependencies.

Issues of relevance across the proposed studies, such as study design including use of alternative study design and analysis, use of placebo or active control, age-appropriateness of endpoints, use of surrogate markers, potential need for short-term and long-term safety studies, and differential risks by age group.

Timelines should be described at a high-level, explaining which studies will be conducted first, in which population and why.

This should be reflected in context of how any uncertainties identified as part of the extrapolation concept (as applicable) are able to be adequately addressed as part of the extrapolation plan which includes the proposed paediatric clinical study(ies). Also, please include cross-reference to other sections as appropriate.

Study <study identifier or number>

Study design

Provide a brief justification of type of study, study design and methodology,

Justification of the dose of the proposed product and its regimen, and the type of control (e.g. placebo or active control, with dose to be used; justification of the proposed duration of treatment, and duration of post-treatment observation if included in the study).

<Text>

Population to be included

This should be consistent with the identified target population in section 2.5. Justification of the relevant age groups or subsets included in the study (and of staggered inclusion where applicable). Justification of main inclusion/exclusion criteria.

<Text>

Choice of control(s)

Discussion on the comparator: placebo as control, or active comparator (authorised, not authorised/standard of care) in phase 3 trials, external control arms, historic controls, etc.

This should be consistent with reflections provided in section 2.

<Text>

<Not applicable>

Sample size

Description of the sample size/power calculation (as appropriate, with expected effect size in children) used to determine the proposed number of subjects (male/female). This discussion should include, where possible, a sensitivity analysis (a tabulation with varying assumptions and statistical parameters, and the resulting sample sizes). If other statistical approaches are used, describe them below.

<Text>

Outcome measures and statistical analysis

Justification of the choice of outcome parameters/endpoints (primary, secondary) their time and justification and, if needed, a more detailed description of statistical methods than that contained in the key elements. Please refer to previous studies as applicable.

<Text>

Comments

|  |
| --- |
| **EMA Scientific Officer:**EMA will insert the proposed clinical study key elements above comments for discussion if necessary and repeat the comment boxes accordingly<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

* 1. Other studies

Provide additional information on other studies proposed, literature analysis, real world evidence sources, etc. that do not fall under the previous sections but are relevant to addressing identified uncertainties as part of the extrapolation plan.

<Text>

Considerations for planned long-term follow-up

Based on the proposed development and the known safety profile, discuss relevant risks that could be important for the paediatric population for which post-authorisation studies are expected. Refer to Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations Chapter IV: Paediatric population: <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-or-population-specific-considerations-iv-paediatric-population_en.pdf>

**This can be reflected in Section 5 of the PDCO Opinion. Despite this information not being part of the PIP commitments, it will support clarifying how any gap in safety profile will be fulfilled.**

<Text>

<Not applicable>

1. Timelines and deferral(s)

This section is not applicable for product-specific waiver applications for all paediatric subsets (full waiver).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study identifier (paediatric study)** | **Population (age group)**  | **Area(quality, non-clinical, clinical)**  | **Date of initiation[[1]](#footnote-2) and deferral requested (Y/N)**  | **Date of completion[[2]](#footnote-3) and deferral requested (Y/N)**  | **Planned regulatory submission** |
| <text> |  |  |  |  |  |

Outline how the plan for paediatric development will integrate into the overall development of the proposed medicinal product and/or the proposed condition/indication(s)in terms of timelines.

Include justification for the proposed timelines of the PIP with respect to planned or ongoing regulatory steps (e.g. marketing authorisation application for indication xyz in adults) and discuss the justification for a deferral (initiation-conclusion) based on the grounds provided by the Paediatric Regulation. Ensure consistency with the GRAPH provided in further section.

Based on the justification and **timelines** described above, state the justification for the **deferral request** in accordance with the grounds of the Paediatric Regulation.

Where it is not planned for a study or other measure in the PIP to be initiated or completed before the submission of the corresponding marketing authorisation application in adults, a deferral may be requested. Requests for deferral should be justified on scientific and/or technical grounds, or on grounds related to public health.

In accordance with the Paediatric Regulation, a deferral will be granted when:

* *it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population; or*
* *studies in the paediatric population will take longer to conduct than studies in adults.*

**Reminder:** in general, a clinical study report (CSR) is required for the PDCO to perform a compliance check. This should be considered in the final timelines of submission.

<Text>

Comments

|  |
| --- |
| **EMA Scientific Officer:**<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

For EMA use only (do not amend or delete)

The following pages are reserved for internal use only however please include references supporting this application on the last page under

“10. References”

1. Paediatric Committee (PDCO) – Discussion

|  |
| --- |
| In MONTH YEAR, the assessment team presented the applicant's proposal, which was reviewed by the PDCO.<Text> |

Additional information received from applicant following Paediatric Committee (PDCO) – Discussion

Only when clarification is requested after PDCO discussion, EMA may insert responses received from applicant in this report.

<Not applicable>

Comments

|  |
| --- |
| **EMA Scientific Officer:**<Text>**PDCO Rapporteur:**<Text>**PDCO Peer Reviewer:**<Text> |

1. Feedback from other EMA committees, working parties or operational expert groups (OEGs)

|  |
| --- |
| <No comments have been requested from other EMA committees, working parties or operational expert groups.><In MONTH YEAR Name of committee, working party, OEG did not identify any outstanding issues.><In MONTH YEAR Name of committee, working party, OEG provided comments on the following issues: * Text>
 |

1. Paediatric Committee (PDCO) - Request for supplementary information and modification of proposed PIP (RSI)

|  |
| --- |
| In MONTH YEAR, the PDCO discussed the application for the paediatric investigation plan and adopted a request for supplementary information and/or modification of proposed PIP (RSI)Include scientific discussion on relevant points (as needed) agreed for the RSI in line with template and current practice. Efforts should be made to focus questions on points that will help shape the opinion.Include outcome of discussions at Committee level.Include general considerations and contributions relevant to the development that were not part of the application.If requested to modify, identify which part, which studies, and which element should be modified, e.g.• Need for age-appropriate formulation.• Acceptability of the proposed formulation (from PDCO point of view).• Need for juvenile toxicity studies or modification of proposed e.g. species.• Agreement and consistency with scientific advice (SA) received.<Text>If applicable, provide information on discussion in the Paediatric Cluster and other international or regulatory interaction.To be drafted after the day 30 discussion, for preparation of the day 60 outcome. Also to be used as contribution to the meeting minutes. Indicate which waiver requests, if any, may be acceptable.**Request for RSI:**Based on the assessment of the application, as reflected in the relevant sections of this summary report and according to the discussions held by the PDCO, the PDCO requests modifications by the applicant, to address the following issues.When responding to this request and amending the PIP, the applicant only needs to address the issues identified below. It is not necessary to address each individual comment identified in this Summary Report, as these do not necessarily reflect the PDCO position agreed on when issuing the request.The Paediatric Regulation accommodates a single clock-stop period, to enable applicants to modify their plans or to submit supplementary information in response to this request. The PDCO will adopt an Opinion on the basis of this supplementary information, without an additional clock-stop period.**Waiver**1. <Text>
2. <Text>

**PIP****Quality**1. <Text>
2. <Text>

**Non-clinical**1. <Text>
2. <Text>

**Clinical**1. <Text>
2. <Text>

**Modelling and simulation, extrapolation and other studies** 1. <Text>
2. <Text>

**Deferral(s) and timelines**1. <Text>
2. <Text>
 |

1. Paediatric Committee (PDCO) – Opinion

|  |
| --- |
| ***Summary of final agreement and on outstanding issues resolved***<Text>Choose from below accordingly***Overall conclusion*****Agreement of PIP:**In MONTH YEAR, based on the assessment of this application and the additional information provided by the applicant, the PDCO adopted a favourable opinion on the agreement of the paediatric investigation plan for the proposed medicine for INCLUDE THE SUBSET OF A PAEDIATRIC POPULATION , in the condition of INCLUDE CONDITION , by consensus.<The PDCO granted a waiver in a subset of children INCLUDE AGE GROUP OF WAIVER on the grounds of INCLUDE GROUNDS .><The PDCO granted a deferral for one or more measures contained in the paediatric investigation plan.>**Refusal of a PIP:**In MONTH YEAR, based on the assessment of this application, the PDCO did not agree with the applicant's proposal for the paediatric investigation plan for INCLUDE CONDITION in children from INCLUDE AGE to INCLUDE AGE as <the measures and the timelines> <the timelines> were not deemed appropriate to ensure the generation of the necessary data to determine the conditions in which the medicinal product may be used to treat the paediatric population or some subsets thereof, or to adapt a paediatric formulation, or the proposed PIP was not expected to generate data supporting an indication of significant therapeutic benefit.**Granting a Waiver:**In MONTH YEAR, based on the assessment of this application, the PDCO <agreed with the applicant's request for a waiver> <agreed a waiver on own motion> by consensus. The PDCO recommended granting a waiver for the proposed medicine for all subsets of the paediatric population (from birth to less than 18 years of age) for the condition INCLUDE CONDITION on the grounds INCLUDE GROUNDS .<The PDCO emphasises that the granting of a waiver for the condition mentioned above should not prevent the applicant from considering a development in the paediatric population in indications where there is a paediatric need. The PDCO identified INCLUDE UNMET NEED as an unmet need. In principle according to the Paediatric Regulation, incentives for the development for use in the paediatric population are available even if a waiver has been granted in another condition.>**Refusal of a waiver:**In MONTH YEAR , based on the assessment of this application, the PDCO did not agree with the applicant's request for a waiver for all subsets of the paediatric population (from birth to less than 18 years of age) in the condition of INCLUDE CONDITION . An opinion on the refusal of a product-specific waiver for the proposed medicine for all subsets of the paediatric population in the condition INCLUDE CONDITION was adopted by consensus.**For all** if applicable<An oral explanation meeting with the Paediatric Committee took place on DATE .> |

1. References

For ALL users

List of references provided by applicant

List of references provided by EMA

<Text>

1. First patient included in trial. [↑](#footnote-ref-2)
2. Last patient, last visit. [↑](#footnote-ref-3)