Briefing book template for Pharmaceuticals

EUnetHTA multi-HTA Early Dialogues

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This template is to be used by companies willing to submit an overview of relevant information necessary to support a EUnetHTA multi-HTA Early Dialogue discussion in the frame of EUnetHTA JA3. *It is not to be used for EUnetHTA Parallel Consultations.*

Standard headings in the template should be used whenever possible. If it is considered necessary to deviate from the pre-specified headings due to product-specific requirements, alternative or additional headings/domains may be considered.

The bracketing convention stated below indicates whether the information to be included is mandatory or optional:

**Bracketing convention:**

*{text}: Required information;*

<text>*: Optional information to be given if applicable;*

*[text]: Explanation and guidance.*

**References convention:**

For citation of literature references, footnotes are preferred, alternatively the format (first author <et al.>, publication year) is recommended.

The document must be submitted in Word format. The recommended length of the briefing book is approximately 50 pages, not including annexes. Any essential self-standing documents such as study protocols, reports etc. should be placed in the annex (section 5 of this template) or should be submitted as separate documents in a Word or PDF format. Referenced articles should be submitted in full text versions.****

Active substance: {}

Product Name: {}

Pharmaco-therapeutic group: {}

Intended indication(s): {}

Applicant (company): {}

Version: {}

Date: {DD/MM/YYYY}

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List of Abbreviations

[Any acronyms or abbreviations used should also be defined the first time they appear in the text.]

# 1. Summary

[It is strongly recommended to address all elements outlined below (whenever applicable) for any advice request, regardless of the scope of the questions. This summary will inform the background information section of the final advice letter. An upper limit of 3 pages for the summary is recommended]

## 1.1. Background information on the disease to be treated

### 1.1.1. Overview of the disease

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[Relevant aetiology, epidemiological data, information on natural history of the disease and evolution of disease symptoms and burden on treatment should be discussed.]

### 1.1.2. Treatment options

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[The company should list all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) and discuss the current standard therapy with regard to the respective labelling status in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development including compassionate use programmes, this information should be included.]

## 1.2. Background information on the product

### 1.2.1. Indication

{}

[The company is asked to specify clearly the intended indication (1st line, 2nd line, 3rd line of treatment; add-on or monotherapy) of the product in development, as well as the aim of treatment (preventive, curative, palliative, symptomatic, disease modifying etc.). The position of the product in the treatment algorithm should be proposed. The target population of the product should be described as precisely as possible.]

### 1.2.2. Characteristics of the product

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[Chemical/biological product; orphan product; advanced-therapy medicinal product, any special precautions or recommendations for use of the product (including a possible risk management strategy)]

### 1.2.3. Form, route of administration, dose, dosage

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[Route of administration and the pharmaceutical form of the product should be described. Dose, frequency of administration and the duration of use should be discussed based on the available evidence at the stage of development.

If the administration of the product is associated with the use of a diagnostic test, a medical device or with a medical procedure, this information should be stated and adequate information given on the associated test or device.]

### 1.2.4. Mechanism of action

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[Pharmaco-therapeutic group should be indicated. ATC code should be given if applicable. The mechanism of action should be described as well as key information on pharmacodynamics and pharmacokinetics.]

## 1.3. Clinical development

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[This section should contain a tabulated summary of completed, ongoing and planned clinical trials as well as post-launch evidence generation (if any planned). Evidence obtained in the field of the required indication should be mentioned. Existence of trials supporting the use of the product in other indications should be mentioned for completeness.]

### 1.3.1. Clinical development up to date

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[Data on efficacy and safety coming from phase I (if relevant) and phase II clinical trials that are completed or ongoing should be presented. For each trial the design, doses and duration of treatment, comparator, number of subjects and description of studied population, results of the trial (or preliminary results of ongoing trials if available) and all other important information should be given. Data and results may be summarized in tables. Detailed information should be available in study reports in annexes. Cross-links to annexes are recommended.]

### 1.3.2. Planned trials

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[This section should provide a comprehensive overview of all planned trials with the product in the intended indication. The company should clearly state which of the planned trials (if there are more than one) will be the subject of the Early Dialogue and a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), comparators, endpoints (primary, secondary, patient reported outcomes (PRO) etc.), flowchart, follow up, sample size estimation, statistical analyses etc. All relevant systematic information should be given at a sufficient level of detail, together with justification for the choice made and a critical discussion of key issues.]

More specifically, the choice of PROs and PROMs should be explained including a literature review of existing PROs in the disease along with justification of the appropriateness of the questionnaire(s) chosen, discussion on Minimal Clinically Important Difference (MCID) and the frequency of collection of these data. If patient preference data are planned to be collected alongside clinical development, detailed methodology should be given.

Provide minimum information on post-launch evidence generation (if planned) for which the developer also requests advice, i.e. anticipated gaps, remaining research questions, high level design of the study, core set of data and data source details if any existing one is planned to be used.

## 1.4. Economic aspects

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[If the company desires to discuss economic assessment as a part of the Early Dialogue, then all relevant information about the planned economic analysis should be provided. The company should state the scope of the planned economic analysis, clearly defining the research questions. The company should describe the main aspects of the economic analysis, in particular the type of analysis, the perspective, the time horizon, the population and the comparator(s).

An outline of the structure of the model could be provided if available. Relevant published papers could be provided as annexes to the briefing book. Expected data sources and planned sensitivity analyses should be described. Trial endpoints used to derive the model health outcome should be stated where relevant. Tools used to measure resource utilization should be described.]

## 1.5. Regulatory status and previous advice

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[Information should be given on the worldwide regulatory status of the product (e.g. any existing marketing authorisation (MA), or planned marketing authorisation application (MAA) timelines), indicating planned type and timelines of MAA (e.g. full/mixed dossier; advanced therapy, biosimilar, generic / hybrid / product) or variation. The company should indicate whether a scientific advice has been received from any regulator (EU, national or non-EU (e.g. FDA) or HTA body and provide minutes or indicate if it is planned at any further stage. Estimated timelines for market entry may be given if this information is available.

If the product has received Orphan Drug Designation (ODD) related to the intended indication, state the orphan indication and the criteria on which the ODD was based.

If applicable, indicate applicability and status of the Paediatric Investigation Plan (with or without deferral or waiver). Indicate availability and need for development in other special populations such as the elderly, male/female and ethnic minorities.]

## 1.6. Rationale for seeking advice

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[The scope of the questions and the rationale for the advice request should be elaborated.]

## 1.7. Discussion on added benefit

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[The company should provide arguments supporting the added benefit of the product in the target population in comparison with the standard of care and with a pharmacologically similar product aimed to be replaced (if adequate).]

# 2. Questions and Applicant’s positions

The company should list all questions they wish to address. It is recommended that questions are phrased in a way to allow for an unambiguous understanding of the question. The scope should be carefully considered in order to avoid too broad or too narrow questions. The wording of questions should be clear and concise, avoiding extended reference to the justifications (which should be discussed in the Applicant position). Open questions are not acceptable. Given the timeframe, a high number of questions (i.e. more than 10) is not feasible to be discussed during the meeting. Questions should be ordered in the corresponding section according to the expertise required for the assessment, and numbered sequentially. Each question should be followed by a corresponding, separate Applicant’s position including a comprehensive justification of the chosen approach. All key information about the topic should be sufficiently discussed, so that the Applicant position can function as a ‘stand-alone’ argument. Issues to be covered could include the following: context and proposal, other options (potentially) considered together with a critical discussion on the relative merits and drawbacks of various approaches, possible consequences and eventual measures to ameliorate these. Each position description should not be longer than 3 pages. Cross-references to the relevant parts of the briefing document or to annexes can be included if additional detail is needed to support the argument.

All scales and scores that will be used for endpoint measurement should be presented and their validity should be commented.]

## 2.1. Questions on Clinical development

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There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

* Population including potential deviation between study population vs targeted indication, biomarkers, subgroups, extrapolation, generalisability…Intervention including dosing, concomitant, addon, monotherapy, duration, label/indication induction, life long therapy…
* Comparator
* Outcomes including primary & secondary endpoints, PROs, Adverse Events (AEs)…
* Study Design including randomisation, duration, statistical methods, time point frequency of data collection…

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Applicant’s position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 3.3.1 Planned trials.]

It is also requested to present questions following the topics described above.

## 2.2. Economic questions

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There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

* Population
* Choice of comparator
* *Intervention and associated health care resource*
* Model structure
* Model assumption and planned scenario
* Model outcomes
* Clinical data and other data sources used to populate the model
* Time horizon and extrapolation hypothesis
* Perspective (societal, healthcare related etc.)
* Utility values
* Collection of resource utilisation data (method and usage)

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Applicant’s position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.2.5 Planned trials.]

# 3. Background information

This section should give a comprehensive scientific overview of the product development program, providing relevant systematic information in sufficient detail, together with a critical discussion. However, it should be kept in mind that any information essential for the justification of a given question should also be sufficiently discussed in the corresponding Applicant’s position. The proposed list of subsections is neither meant to be exhaustive nor mandatory, since the relevance or applicability of each subsection may vary depending on the scope of the advice request. In this respect, the potential direct or indirect relevance of the information covered in relation to the questions posed should be considered. Additional details can be included in study protocols, study reports, investigators’ brochure provided as annexes. The use of tabulated overviews and graphs is encouraged.]

## 3.1. Clinical efficacy

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[A general overview of the clinical development program should be based on a comprehensive discussion of e.g. the main clinical results so far, dose-response, exploratory trials, special populations, supportive and pivotal clinical studies, and any analyses performed across trials (pooled and meta-analysis). The discussion should identify the most important findings and challenges in the clinical development program, and its compliance with legal requirements, relevant clinical guidelines, previous scientific advice (sufficiently justifying any deviations), etc. Information on the geographical distribution of centres participating in the pivotal clinical studies can be reflected in this section.]

## 3.2. Clinical safety

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[A general overview of the safety profile of the product should be based on a comprehensive discussion of e.g. patient exposure (safety database), adverse events observed so far, serious adverse events and deaths, laboratory findings, safety-related discontinuations, specific safety findings, immunological events, safety in special populations, etc.]

## 3.3. Post-Launch evidence generation

Any planned post-launch evidence generation should be detailed as much as possible. Data can derive from trials or from a wide range of other sources (e.g. medico-adm, claims records, health care records) or data capture mechanisms (e.g.registries, from wearable devices or smartphone apps). A minimum information on research question, high level on study design and detailed description of the source when one is identified.

## 4.4. Economic assessment

[• The company should state the scope of the planned economic analysis, clearly defining the research questions. Evidence gaps and model assumptions should be described.

If plans for the economic evaluation are provided, these should include to the extent possible:]

<• Description of the proposed model (diagram, modelling approach, time horizon, perspective)>

<• Data collection plans to inform the model:

- Evidence synthesis/meta-analysis – sources of evidence

- Comparators – MTC and indirect comparisons and evidence available

- Trial endpoints used to derive health outcomes in the model

- Quality of life – source and methods, tools used to measure quality of life

- Incorporation of adverse effects

- Resource use – sources and methods, tools used to measure resource utilisation>

<• Methodological Approaches:

- Extrapolation – assumptions and data sources

- Continuation rules

- Use of surrogate outcomes

- Planned sensitivity analyses]>

# 4. List of References

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[In general, any potentially relevant publications included in the list of references should be annexed (in PDF format, either collated as a single document or if provided as single files, clearly identified and whenever possible compiled in one or more compressed files, for convenience). In case a relevant publication is not included at the time of validation, it should be ensured that it can be made available upon request.]

# 5. List of Annexes

[Annexes should include any information potentially relevant to the questions, e.g.

* Investigators’ brochure
* Study protocols (final, draft or outline/synopsis)
* Study reports (final/draft/synopses)
* Previous scientific advice received (e.g. CHMP Scientific advice/Protocol Assistance, any relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities)
* Relevant guidelines (EMA and non-EMA)
* Contract/agreement consultant/CRO - sponsor
* Referenced articles in full text versions in English

# 6. Contact point

Any question or comment concerning this document or any other point related to the Early Dialogues conducted in the frame of EUnetHTA JA3 should be sent to [eunethta-has@has-sante.fr](mailto:eunethta-has@has-sante.fr) .