# Health technology assessment process guidance – medicinal products

# Contents

## Acknowledgements

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## Glossary

A complete glossary for terms for health technology assessment (HTA) have been one of the key deliverables for the SUSTAIN-HTA project. SUSTAIN-HTA is a Horizon Europe initiative that builds a sustainable, pan-European infrastructure to support the uptake of innovative, fit-for-purpose HTA methods. It identifies HTA bodies' methodological needs, maps innovative tools, and strengthens HTA expertise through training, education, and targeted support.

The SUSTAIN taxonomy provides a comprehensive, standardised classification of 374 HTA-related terms across key assessment, regulatory, and decision-making domains to support consistent communication and methodological alignment. It was developed through a targeted review of EU HTA documents, extraction and analysis of terminology, and consensus-building among SUSTAIN-HTA partners from multiple HTA bodies and academic institutions.[1] Tarang Sharma, Technical Officer, Access to Medicines and Health Products, WHO Regional Office for Europe) is part of the Expert Advisory Group for the SUSTAIN-HTA project.

The SUSTAIN-HTA Taxonomy tool is available here which has a complete glossary of relevant terms used in this document: https://bu2f97-saifelayan.shinyapps.io/appd/

[1] Elayan S, Goettsch W, Facey K, Garrett Z, Elvidge J, Collins S, Oortwijn W, van Mun L. SUSTAIN-HTA D1.1: Taxonomy report. Utrecht (NL): SUSTAIN-HTA Consortium; 27 June 2024. Available from: https://sustain-hta.org/wp-content/uploads/2025/04/SUSTAIN-HTA_D1.1_Taxonomy-report.pdf

# 1. Introduction

## 1.1 Background and context

Health technology assessment (HTA) is defined by the European Union (EU) as a scientific, evidence-based process used by competent authorities to evaluate the relative effectiveness of new or existing health technologies *(1)*. The primary goal of HTA is to assess the added value of a health technology in comparison to other alternatives, thereby supporting informed decision-making in health care.

Greece first introduced its HTA system in January 2018, with implementation beginning in mid-2018 *(2)*. This marked a significant development in national health policy, particularly in the area of reimbursement decisions for medicinal products. HTA serves as a strategic tool to ensure efficient use of limited resources, facilitate timely patient access to innovative therapies, and support the sustainability of the health-care system through cost-effective investment in new technologies.

Regulation (EU) 2021/2282 on health technology assessment (the EU HTAR) entered into force on 11 January 2022 and applies from 12 January 2025 *(1)*. It establishes a common framework and procedures for cooperation of EU Member States on health technologies, as well as common rules and methodologies for assessing health technologies. The EU HTAR identifies four areas of joint work.

- **Joint clinical assessment** (JCA) is defined in the EU HTAR as "the scientific compilation and the description of a comparative analysis of the available clinical evidence on a health technology in comparison with one or more other health technologies or existing procedures, in accordance with an assessment scope agreed pursuant to this Regulation and based on the scientific aspects of the clinical domains of HTA". The assessment scope refers to the "patient population, intervention, comparators and health outcomes requested jointly by Member States" (Article 2).
- **Joint scientific consultations** are conducted "to exchange information with health technology developers on their development plans for a given health technology. Those consultations shall facilitate the generation of evidence that meets the likely evidence requirements of a subsequent joint clinical assessment on that health technology" (Article 16(1)).
- One area of focus is identification of **emerging health technologies**, particularly to address "the estimated clinical impact and the potential organisational and financial consequences of emerging health technologies for national healthcare systems" (Article 22(1)).
- **Voluntary cooperation on HTA** refers to cooperation and exchange of scientific information among Member States on, among others, non-clinical assessments, collaborative assessments on medical devices and in vitro diagnostic medical devices, and HTAs on other types of health technologies than those within the scope of the EU HTAR (Article 23).

JCAs will first consider new medicines such as cancer therapies and advanced therapeutic medicinal products, followed by certain high-risk medical devices and in vitro medical devices and then orphan drugs from 13 January 2028 and all new medicines, from 13 January 2030.

## 1.2 Aim and scope of the guidance

The purpose of this publication is to guide the process of HTA used in assessment and reassessment of medicinal products in Greece, such that it is aligned with the EU HTAR.

Implementation of the EU HTAR, which came into force on 12 January 2025, represents a major milestone for Greece and all EU Member States. In response, Greece has been updating its HTA governance, legislation and institutional capacity to ensure alignment with EU HTAR requirements. This guidance reflects those developments. It builds on the HTA framework established in 2018, and supports Greece's alignment with the EU HTAR, contributing to HTA and reimbursement decisions that are transparent, consistent and evidence-informed.

This guidance currently considers HTA for medicinal products for both:

- when complete national HTAs need to be conducted; and
- when JCAs are available for the clinical assessment, and only economic and other considerations need to be assessed at the national level.

## 1.3 Target audience

This guide is intended for stakeholders involved in HTA in Greece, including health technology developers, clinical professionals, patient representatives, payers, the academic community and decision-makers. It is particularly relevant for those national decision-makers conducting or using HTA to inform pricing and reimbursement decisions and procurement of medicinal products.

## 1.4 How this guidance was developed

This process guidance will form the national framework for HTA in Greece alongside the methodological guidance for HTA. It was developed through an iterative, collaborative process led by the Greek Ministry of Health, the Greek HTA Committee, the WHO Regional Office for Europe and the European Commission's Technical Support Instrument.

The evaluation of a health technology may be conceptualized as comprising five distinct steps. This guidance addresses the last three process components; the first two steps are detailed in the accompanying methodological guidance:

- scoping or problem definition
- analysis of the evidence (assessment)
- appraisal
- decision-making
- implementation and monitoring.

The development process began with a comprehensive situation analysis of Greece's HTA landscape *(3)*, aimed at identifying gaps, capacity needs and challenges in aligning with the new EU HTAR. This phase involved an extensive literature review, in-depth stakeholder interviews and targeted consultations, as well as a detailed examination of the EU HTAR documents.

Building on the insights from the situation analysis, the second phase focused on developing updated draft methodological and process guidance for the Greek HTA framework. This effort drew on international best practices and expert input from leading HTA agencies in

France (Haute Autorité de santé), Italy (Agenzia italiana del farmaco), Portugal (Infarmed) and the United Kingdom (National Institute for Health and Care Excellence), and from the WHO Collaborating Centre for Pharmaceutical Policy and Regulation at the University of Utrecht, Netherlands (Kingdom of the). A combination of virtual engagements and in-person site visits facilitated identification of effective approaches and their adaptation to the specific needs and context of the Greek health-care system.

Robust stakeholder engagement has been a cornerstone of the development process, ensuring transparency, inclusivity and shared ownership in the effort of strengthening Greece's HTA system. Key stakeholders involved in the development of this guidance include the Greek Ministry of Health, the Greek HTA Committee, the National Organization for the Provision of Health Services (EOPYY), health-care professionals, academia, a scientific advisory group, industry representatives and – critically – patient groups (who are also part of the high-level steering committee). Ensuring that patient voices are heard remains a core principle of the HTA process.

## 2. Governance and structure

The governance and structure of HTA in Greece was considered in detail through a project conducted by another vendor (Agreement: Provision of technical support, maturation, monitoring of actions and projects and programme management (PMO) services as well as advisory services for the support for the implementation of Recovery and Resilience Fund projects; Deliverable 491: Implementation of the Health Technology Assessment (HTA) Agency), submitted to the Greek Ministry of Health in May 2025.

That study included a questionnaire based on relevant literature, a consultation meeting and an analysis of strengths, weaknesses, opportunities and threats; it gathered input from institutional, scientific and other stakeholders to shape the proposed HTA structure. This HTA body will represent a strategic initiative aimed at enhancing the efficiency, transparency and evidence-based nature of health-care decision-making in Greece. Its primary purpose will be to assess and integrate new health technologies – including pharmaceuticals, medical devices and innovative therapies – into the national health system. This initiative aligns with core principles of effectiveness, efficiency and equity, and reflects a broader commitment to rational resource allocation and high-quality health policy.

Structurally, the HTA body is envisioned as a small, flexible, not-for-profit organization, unit or department, staffed by a multidisciplinary team of experts such as health professionals, epidemiologists, health economists, clinical pharmacologists, data scientists and legal experts. It will be governed by scientific and management boards and organized into dedicated sections for evaluation, pricing, reimbursement and health economics. This HTA body may comprise current HTA Committee and Negotiation Committee members, external assessors and other academic experts in the field of HTA. It will operate with a staff size of 11–50 people, and will be funded through a combination of government budget allocations, submission fees from health technology developers and revenue from additional activities. Until such a body is established, the process will be implemented by the HTA Committee and Negotiation Committee.

The role of the HTA Committee is to:

- appraise the clinical evidence and determine the added therapeutic value of the health technology in comparison to relevant alternatives;
- appraise the other considerations, including ethical, legal, social, feasibility and organizational aspects;
- contextualize the scientific evidence within the Greek health-care system and population needs;
- ensure that recommendations are transparent, evidence-informed and consistent with the accompanying methodological guidance; and
- consider clinical expert and patient input in the appraisal and deliberation process.

The role of the Negotiation Committee is to:

- appraise the economic evidence, including cost–effectiveness, budget impact and affordability;
- consider the feasibility of implementation, including pricing structures, reimbursement conditions and managed entry agreements; and
- formulate pricing and reimbursement recommendations to the Minister of Health.

The HTA process will be initiated by health technology developers, and will follow transparent procedures – including consultations and clearly defined roles for clinicians, patients and developers. Assessment reports and recommendations will be published on a dedicated public HTA website to ensure transparency. An assessment-specific HTA Committee will be established for each submission whose members will be independent and will serve for limited terms. The HTA body will be open to strategic collaborations with universities, international HTA organizations, patient associations, and other stakeholders, possibly through collaborating centres. Diverse expertise will be reflected in the HTA Committee, including that of a generalist member of a patient or carer organization, or other organization representing national health service users, enabling input that is independent of any specific HTA. The HTA Committee will be responsible for appraisal and making recommendations based on the clinical evidence, while an independent Negotiation Committee will be responsible for appraisal and making recommendations made based on the economic evidence.

Implementation of this HTA body requires a formal political decision, followed by a participatory consultation process and establishment of a coordination and monitoring group. The administrative setup will involve defining the institutional placement of the HTA body, adjusting the organizational structure of the host institution, and aligning procedures with the EU HTAR.

The long-term vision includes building strategic partnerships at both national and international levels to ensure that the Greek HTA body remains adaptive, credible and impactful in the evolving health-care landscape.

## 3. Stakeholder involvement

In accordance with the EU HTAR requirements, and as gap identified by the situational analysis, a formal stakeholder involvement process is needed in Greece. Experts will be selected based on the specific HTA topic and their clinical or patient experience relevant to the condition or technology under assessment, and will be remunerated for their

contributions. Stakeholders should be involved in at least at two key stages of development, at the population, intervention, comparator, outcome (PICO) and scoping stages, as well as at the consultation stage for the draft assessment report. They can also provide both written and verbal contributions as needed and appropriate, including at HTA Committee meetings. To ensure timely input and feedback from stakeholders, the annual horizon scanning list of potential submissions from health technology developers for the coming year will be shared with the registered clinical expert pool which are part of the EOF registry, and with registered patient organizations.

Appropriate staffing should be considered for managing stakeholder involvement within the HTA body, such that it can be handled and managed with sufficient quality and rigour. The individual leading the stakeholder involvement needs to work closely with the legal team of the HTA body to ensure compliance with any conflict of interest (COI) requirements (see section 3.5). Regular training in methods and processes will be provided to the clinical and patient experts to safeguard the quality and rigour of the process, and to ensure that they can contribute actively to the development of the HTA.

To increase transparency and facilitate general understanding of the process with the broader public in Greece, all proposed and final PICO data, as well as a plain-language summary of the assessment report, will be made available on the dedicated public HTA website (with all confidential information redacted as notified by the developer).

## 3.1 Clinical professional involvement

Greece already has a good pool of registered clinical experts. For each assessment, 2–3 topic-relevant clinical experts can be selected to support the HTA from the existing pool – based on their clinical background and relevance to the specific topic being considered – by the proposed HTA body . Once relevant experts from the pool are identified, confirmation of their appointment requires any COIs (see section 3.5) to be checked and confirmed. The clinical experts appointed and any declared COIs will be made available on the dedicated public HTA website.

## 3.2 Patient involvement

All the relevant registered umbrella patient associations will be contacted by the proposed HTA body, depending on their background and relevance to the specific topic being considered. The relevant umbrella patient associations will contact their members to identify relevant individual patient experts to participate in the process. For each assessment, 2–3 topic-relevant patient experts can be selected by the proposed HTA body to support the HTA. Once relevant experts from the umbrella patient associations are identified, confirmation of their appointment requires any COIs (see section 3.5) to be checked and confirmed. For certain conditions and topics, carers rather than the patients themselves may also be considered appropriate. The patient experts appointed and any declared COIs will be made available on the dedicated public HTA website.

## 3.3 PICO data and scoping

The PICO framework is a fundamental step in scoping HTAs. Engaging relevant stakeholders, including clinical experts and patients, ensures that the PICO reflects clinical relevance and patient-centred perspectives.

The initial indication and draft PICO report submitted by the health technology developer (see Annex 1) will be reviewed by the proposed HTA body, which will select experts (clinical and patient) from the clinical pool and from registered patient organizations (see section 3.2). Once the experts have cleared the COI requirements and are appointed, a PICO questionnaire will be submitted to them to consider the parameters relevant to the Greek context, ensuring they are given a minimum of 10 days to provide input. The HTA body will have up to four weeks from submission of the draft PICO report from the developer to submit its amendments, with input from the clinical and patient experts. The HTA body will submit its final PICO report to the health technology developer to develop the HTA dossier, including consultation with the HTA Committee if needed. There will be a formal meeting with the HTD and HTA assessors regarding the updated PICO to arrive at the final PICO and further discussions if deemed appropriate by both parties.

## 3.4 Draft consultation

The proposed HTA body will review the dossier submitted by the health technology developer and prepare a draft assessment report – with input from the clinical and patient experts as needed for any clarifications. Once a draft report on the clinical evidence is ready, a thorough consultation will be undertaken by the appointed clinical and patient experts, who have four weeks to review it.

Comments from the experts will be considered by the HTA body and by the external HTA Committee, and an updated report incorporating the expert input and draft recommendations developed by the HTA Committee will be submitted to the developer (see section 5). At this stage, a formal discussion meeting can also take place between the developer and HTA Committee, including HTA assessors, patients and clinicians, to permit discussion and dialogue between the parties as necessary.

The health technology developer will have four weeks to review the report and send any clarifications to the HTA body and HTA Committee, primarily to address factual errors and to mark any information considered confidential within the report. The HTA body can then update the assessment report as appropriate, after which the HTA Committee and Negotiation Committee will make final recommendations and prepare a final assessment report. A plain-language summary of the report will be published on the dedicated public HTA website for transparency (with all confidential information redacted as notified by the developer).

## 3.5 COIs

All experts consulted as part of the HTA process must complete COI declarations to ensure transparency. These will be reviewed by the HTA body to identify suitable candidates based on conflicts declared. COI declarations will be published on the dedicated public HTA website to maintain transparency.

The HTA body will manage declared COIs through proportionate mitigation measures, rather than automatic exclusion. This may include:

- Balanced committee composition, ensuring that no single expert or interest dominates deliberations, including the inclusion of members without relevant COIs where available.

- Restriction of participation in specific parts of the HTA process, such as recusal from discussions or decisions relating to pricing, reimbursement conditions, or final recommendations.
- Advisory-only roles for experts with relevant COIs, without voting or decision-making authority.

The management approach will be proportionate to the level of risk posed by the declared interest and documented by the HTA body.

The COI standards for Greece are being considered in the light of the EU HTAR, and updates are being made to align with guidance at the EU level. It is important to consider that flexibility maybe needed for rare and ultra-rare conditions: COIs may be declared and then their influence mitigated in the decision-making process if no clinical or patient experts without COIs are available. Flexibilities may also be required for products designated as PRIority Medicines (PRIME) by the European Medicines Agency (EMA).

### 3.6 Alignment with the European JCA and joint scientific consultation processes

When the HTA topic is scoped through the JCA process at the EU level, the proposed PICO from the health technology developer will be shared with Greece through the lead and co-lead assessor agencies for that JCA. Input from Greek clinical and patient experts will be sought using the same PICO questionnaire to incorporate the Greek health-care context and perspective (keeping the timeline limitations in mind). This input will also be sought at the draft JCA consultation stage – once again keeping the timeline limitations in mind.

For joint scientific consultations, the HTA body can also request expert input from clinicians and patients to ensure that Greek perspectives and requirements are included appropriately in the development of the scientific evidence by developers.

## 4. Assessment of clinical, economic and other considerations

Scientific (clinical and economic) assessment involves collection and synthesis of evidence. It is a research-based, objective activity that provides the scientific basis for decisions on the efficient and appropriate use of resources. Assessment is based on an explicit methodology that places importance on the traceability of the (clinical and economic) evidence and on independence from all relevant interest groups to avoid undue influence.

Clinical assessment of the dossier submitted by the health technology developer (see Annex 2 and 3) will be conducted by the HTA body in accordance with the accompanying Greek HTA methodological guidance (see section 1.4). A full cost-effectiveness evaluation will only be required if a medicinal product is deemed to have major, substantial or moderate added therapeutic value at the clinical assessment stage. However, the health technology developer may opt to submit a full cost-effectiveness evaluation in advance of the HTA Committee's clinical assessment regarding added therapeutic value.

When a medicinal product offers no added therapeutic value, a cost-minimization or cost-comparison analysis may be employed to ensure efficient resource allocation. An assessment of the economic evidence submitted by the developer (see Annex 4) will be

conducted by the HTA body in accordance with the Greek HTA methodological guidance. If the health technology developer opts to submit the clinical and economic evidence in sequence, the official process will include a “clock stop” to allow the developer to create an economic dossier after the clinical assessment recommendations are made.

## 4.1 Technical validation

The HTA body will carry out a technical validation of the application by reviewing the materials to ensure that all the specification requirements have been met. The validation process includes checking whether the application form has been completed correctly with relevant information and source references, and whether the health economic analysis has been submitted in Excel format with the option to change relevant parameters. All inputs in the model must be fully editable; in the event of changes, the model must automatically update all the results, sensitivity analyses and so on.

The health technology developer must state as promptly as possible when it expects to submit a new or updated application, to aid planning by the HTA body and the HTA Committee. To facilitate effective planning and scheduling, a minimum advance notice of two months prior to resubmission is recommended. The developer will be notified about whether the application can be approved and considered satisfactory as soon as possible – within seven business days. If the application is not approved, a brief explanation will be attached to the notification.

If the developer submits an amended application, the HTA body will start a new technical validation. Day 0 is the day the HTA body receives the first complete PICO application dossier. Official clock stops will be made when the proposed HTA body or the HTA Committee requests additional information from the developer during the process, until that additional information is received and validated.

## 4.2 Assessment report

The HTA body will be able to draw on the expertise of the clinical and patient experts as needed for any clarifications during the development of the assessment report, but a thorough consultation with the appointed clinical and patient experts will be done once a draft report is ready (see Annex 5 and 6). Patient groups participating in the assessment process will have the opportunity to present how their lives are affected by the disease and what a new therapy might do to improve their condition. Patient perspectives may be taken into account indirectly through safety, effectiveness and quality-of-life measures, but such indicators may not adequately reflect important broader values such as preference for one treatment over another, or acceptability of various side-effects. The health technology developer will also have an opportunity to review the draft assessment report (see section 3.4).

For further details on the methods used by the HTA body to develop the assessment report see section 3 and the accompanying methodological guidance (see section 1.4). A plain-language summary of the final report will be published on the dedicated public HTA website (with all confidential information redacted as notified by the developer). The assessment report will be appraised by external independent committees, which will be responsible for making recommendations to the Minister of Health, who will make the final decision (see section 5).

### 4.3 Alignment with the EU JCA process

HTA topics in Greece will be considered in line with the EU HTAR specifications, and only those not included within the Regulation's roll-out plans (see section 1.1) will go through a full national process. WHO is developing a framework that will be a structured, stepwise approach to guide evidence-informed priority-setting in health, including for HTA, which can be used to guide Greece. It includes eight key steps: prepare the groundwork, refine the scope, implement the assessment, organize the appraisal, recommend actions, implement decisions, translate and uphold entitlements, and evaluate and sustain progress.

When the HTA topic is considered through a JCA at the EU level, the HTA body will consider the JCA for the clinical element but will also request the health technology developer to submit the sections of the dossier on economic and other considerations for the Greek context for assessment and appraisal.

## 5. Appraisal and decision-making

Appraisal involves judgement and valuation of one or more of the clinical, economic, ethical, legal, social, feasibility and organizational aspects of a technology by contextualizing the evidence submitted and formulating recommendations on the appropriate use of resources.

Appraisal focuses on quality of evidence and contextualization, and considers the wider impact of a health technology on society and on a country's health (and economic) system. Clinical evidence will be appraised by the external HTA Committee, while economic evidence will be appraised by the independent Negotiation Committee. The appraisals will be based on the draft assessment report developed by the HTA body that considers the dossier submitted by the health technology developer (see section 4). The HTA Committee will appraise the other considerations (ethical, legal, social, feasibility and organizational aspects) and consider those as relevant for their deliberations during appraisal committee meetings to make their recommendations. Membership of the committees will be published on the dedicated public HTA website, along with any COI declarations. (See section 2 for further information on governance and structure.)

### 5.1 Appraisal preparation

The HTA body will prepare all the necessary documentation for the committees to appraise the evidence at their meetings. This includes the agenda for the day, the draft assessment report, the original health technology developer's dossier, any feedback and input from the clinical and patient experts, and relevant COI declarations.

### 5.2 Appraisal committee meetings and recommendations

Appraisal committee meetings will enable independent deliberation on the draft assessment report developed by the HTA body. They will use the explicit and transparent domains of clinical, economic (including budget impact and affordability issues), ethical, legal, social, feasibility and organizational aspects of a technology as described in the report, in line with the accompanying methodological guidance (see section 1.4). Clinical input and patient perspectives are also considered; if deemed important, committees can call for verbal expert testimonies at their meetings. This facilitates appropriate consideration of elements such as disease severity, unmet need, and equity and legal aspects.

To ensure transparency of appraisal committee meetings, agendas and minutes of the meetings – as well as a plain-language summary of the assessment report (with all confidential information redacted as notified by the health technology developer) – will be published on the dedicated public HTA website. All COI declarations and attendance will be formally recorded and noted within the minutes for each meeting.

The first appraisal committee meeting of the HTA Committee will discuss the clinical and other considerations contained in the draft assessment report which has been reviewed by the health technology developer (see section 3.4). If substantial changes are made by the HTA body in line with the input, a second appraisal committee meeting may be needed to make final recommendations.

Many countries have developed social value judgements that guide decision-making and the appraisal process *(4,5)*. Greece does not currently have such a set of judgements; if one is developed, it should be considered by the committees to guide the appraisal process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision framework for coverage decisions *(6)* provides further guidance. It sets out a framework for consideration of all forms of evidence together – including values and preferences – to make draft recommendations for coverage decisions *(7)*. The GRADE framework suggests criteria to support systematic and transparent decisions (Table 1).

**Table 1. Grade framework criteria and questions**

| Category | Questions |
|---|---|
| Problem | Is the problem of priority for the population? |
| | How important is the health issue being addressed? |
| Benefits | What are the desirable anticipated effects of the intervention? |
| | How substantial are the benefits? |
| Harms | What are the undesirable anticipated effects? |
| | Are there significant risks or adverse outcomes? |
| Certainty of evidence | How confident can decision-makers be in the evidence of benefits and harms? |
| | Is the evidence of high, moderate, low or very low certainty? |
| Values | How much do people value the main outcomes? |
| | Is there variability or uncertainty in how outcomes are valued? |
| Balance of effects | Do the desirable effects outweigh the undesirable ones? |
| | Is the net benefit clear? |
| Resource use | What are the costs of the intervention? |
| | Is it a good use of resources? |
| Certainty of evidence on resource use | How confident can decision-makers be in the cost estimates? |
| | Are the economic evaluations robust? |
| Cost–effectiveness | Is the intervention cost-effective? |
| | Does it offer good value for money? |
| Equity | What would be the impact on health equity? |
| | Would the intervention reduce or increase disparities? |

| Category | Questions |
|---|---|
| Acceptability | Is the intervention acceptable to stakeholders (patients, providers, payers)? |
| | Are there concerns about social or political acceptability? |
| Feasibility | Can the intervention be implemented in the current system? |
| | Are there barriers to implementation? |

The final recommendations from the HTA Committee and the parts of the draft assessment report related to economic and other considerations will be considered by the Negotiation Committee at another appraisal committee meeting. This Committee will make recommendations on pricing and reimbursement decisions and begin negotiations with the health technology developer.

The Negotiation Committee will appraise the evidence using explicit and transparent criteria, including:

- cost-effectiveness and value for money;
- budget impact and affordability for the national health system;
- uncertainty in the economic evidence;
- feasibility and sustainability of reimbursement;
- potential use of conditional or managed access agreements.

Possible types of recommendations include:

- recommended as applied for (routine use);
- recommended with restrictions (for example, for a specific subpopulation or line of therapy);
- recommended only in the context of a conditional reimbursement agreement (see section 8); and
- not recommended (with rationale and justifications provided).

The Negotiation Committee's recommendations will be documented, including the rationale, and submitted together with the HTA Committee's recommendations to the Minister of Health for the final decision.

## 5.3 Final decision

All final recommendations from the assessments of the HTA Committee and the Negotiation Committee will be submitted jointly to the Minister of Health, who will make the final decision. The recommendations by the HTA and Negotiation committees are not legally binding, but they are normally followed unless there are specific reasons not to do so; these will be communicated to the relevant stakeholders by the Ministry of Health.

A plain-language summary of the assessment report will be developed by the HTA body, and will be published on the dedicated public HTA website for transparency (with all confidential information redacted as notified by the health technology developer). The dedicated public HTA website will contain:

- the membership of both the committees and any COI declarations;
- the agenda and minutes of all appraisal committee meetings; and

- for every individual HTA:
    - the final PICO report;
    - the list of clinical and patient experts and any COI declarations;
    - the plain-language summary assessment report (with all confidential information redacted as notified by the health technology developer).

The full process from submission by the developer of the dossier considered complete in the validation phase (Day 0) until a final decision has been made by the Minister of Health should take a maximum of six months, in accordance with the EU Transparency Directive *(8)*.

# 6. Appeals process

The appeals process is guided by principles of enabling fairness and transparency, but should not stall implementation of HTA recommendations. It is intended to ensure procedural and evidentiary fairness. An appeal in administrative courts can be made the Minister of Health to reconsider its decision 45 days following the final decision by any relevant stakeholder. This includes either the applicant health technology developer or other stakeholders, such as clinicians and patient groups, where they are directly affected. Grounds for appeal include disagreement substantiated by evidence (scientific evidence or evidence of flaws in the procedures followed), such as procedural errors, disagreement with the committees' rationale or interpretation of the evidence.

The appeal process should be managed independently of the HTA body that undertook the assessment and appraisal processes to ensure fairness, but the Ministry of Health can ask the HTA body for additional evidence and/or call an additional appraisal committee meeting from one or both committees, as appropriate.

Timely settlement of appeals (typically within 30–45 days) is essential in order that a recommendation (assessment and appraisal) and a funding decision on a new medicinal product can continue to comply with the EU Transparency Directive timelines.

The outcome of an appeal (uphold, revise or reappraise) and the accompanying rationale for the outcome should be published in summary form on the dedicated public HTA website.

# 7. Implementation and monitoring

## 7.1 Implementation

EOPYY is the central public health insurance body in Greece. It was established in 2011 to centralize and streamline insurance funds and access to health-care services. EOPYY is responsible for implementation of the recommendations made by the HTA Committee and the Negotiation Committee.

It is crucial that the time between the committees' recommendation and the final decision by the Minister of Health and their implementation is as short as possible to ensure timely access for patients. Therefore, EOPYY needs to take the necessary administrative and contractual steps to ensure incorporation of approved health technologies into the benefits package, reimbursement systems and purchasing agreements for procurement, including collaboration with relevant agencies such as the e-Government Center for Social Security (IDIKA).

The Ministry of Health is also responsible for overall implementation owing to its authority over protocols, registries and public hospitals in Greece.

### 7.2 Monitoring, reassessment and reappraisal

HTA in Greece will be guided by up-to-date scientific evidence, international standards and national health priorities. It will also be revised in accordance with experience gained in the process. A regular reviewing process ensures that the medicinal product continues to deliver value, and addresses uncertainties relevant to the HTA body and payers.

Monitoring and evaluation of the HTA decision can be done through key indicators such as uptake, adherence, real-world patient outcomes on efficacy, longer-term safety measures and budget impact on the health system. Routine data sources such as patient registries and electronic health records can be used for monitoring purposes.

At a minimum, the recommendations should be reviewed every five years to ensure relevance. They can also be reviewed earlier for one of the following reasons:

- when new evidence of safety, effectiveness and cost–effectiveness accumulated in subsequent trials, meta-analyses, post-market surveillance, audits, registry data, is made available;
- following implementation of a term-limited conditional or managed access agreement (see section 8);
- following a resubmission by the health technology developer on receiving a negative decision with additional evidence and/or pricing amendments; or
- following an appeal by a stakeholder to the Minister of Health.

In all cases, a new or updated assessment report will be developed by the HTA body using the same methods, processes and principles as the initial assessment, and will probably require new appraisal committee meetings. The reassessment and reappraisal process may lead to new or amended recommendations by the committees and decisions by the Minister of Health.

## 8. Conditional reimbursement fund and process

Establishment of a conditional reimbursement fund in Greece was considered in detail through another project (Agreement: Provision of technical support, maturation, monitoring of actions and projects and programme management (PMO) services as well as advisory services for the support for the implementation of Recovery and Resilience Fund projects; Deliverable 491: Implementation of the Health Technology Assessment (HTA) Agency). This project was developed by Price Waterhouse Coopers (PwC) and as part of the broader EU Recovery and Resilience Fund framework. It aims to address systemic challenges in pharmaceutical expenditure, improve patient access to innovative treatments, and align Greece with best practices in Europe. The Fund is designed to support early access to advanced therapy medicinal products and priority medicines, bridging the gap between European Medicines Agency approval and national reimbursement.

The PwC project aimed to harmonize Greece with EU practices and establish a stable, transparent and fair framework for cooperation with the pharmaceutical industry, ensuring sustainable access to innovative treatments. The project contextualizes the need for reform in Greece's pharmaceutical landscape, citing the high proportion of pharmaceutical

expenditure relative to total health spending, and delays in patient access to new treatments. It highlights the structural inefficiencies in the current system, including the clawback mechanism and the lack of a dedicated framework for managing innovative therapies.

The PwC project proposed an innovation fund as a transitional compensation mechanism that would allow incorporation of real-world evidence, outcome-based evaluation and managed financial risk, thereby improving transparency and sustainability through systematic managed entry agreements. The project undertook a detailed comparative analysis of innovation funds in England, United Kingdom, and Italy, showcasing governance models, evaluation criteria, funding mechanisms and implementation procedures. England's Cancer Drugs Fund and Innovative Medicines Fund emphasize managed entry agreements and cost–effectiveness thresholds (such as evaluations based on quality-adjusted life-years), while Italy's Agenzia italiana del farmaco Innovation Fund focuses on therapeutic need, added value and evidence quality using the GRADE methodology. These models informed the proposed structure for Greece, which aims to combine rigorous evaluation with flexible funding and stakeholder collaboration.

The Greek Ministry of Health and core members of the Greek HTA Committee and Negotiation Committee also received training on managed entry agreements through the United Kingdom's National Institute for Health and Care Excellence and the WHO Collaborating Centre for Pharmaceutical Policy and Regulation at the University of Utrecht, Netherlands (Kingdom of the), via WHO's Access to Novel Medicines Platform *(9)*. The principles of managed entry agreements, the checklist and ground principles and templates can be used to facilitate this work.

The proposed Greek conditional reimbursement fund includes a governance framework under the Ministry of Health, with operational support from EOPYY and the National Organization for Medicines. It proposes that medicines be evaluated based on effectiveness, safety and resource consumption indicators over a specific period – typically up to 36 months, with reassessments. This process would facilitate collection of real-world evidence to address clinical uncertainties and inform long-term reimbursement and pricing decisions. Funding sources would include: the Ministry of Health's pharmaceutical expenditure budget, savings from the Institute of Pharmaceutical Research and Technology channel, prescription fees, percentage fees from clinical trials and donations. The fund is designed to be financially sustainable, with mechanisms to prevent budget overruns and ensure equitable access.

The health technology developer can consider submitting a value of information analysis, including an expected value of perfect information analysis for products being considered for this fund.

## 9. Other related aspects

The health technology developer can also request early scientific advice from the HTA body on development of their evidence to ensure that the perspectives of the Greek context are included in the clinical development pathway early on. Such services can help to clarify how to generate robust evidence that demonstrates the value of a new medicinal product in Greece. Standard charges and fees will apply to the developer for each HTA assessment (at PICO and dossier submission stages), as well as for scientific advice. Recommendations from early scientific advice given are not binding for the clinical assessment.

The assessment reports from any HTA should play a pivotal role in guiding Greek national clinical guidelines by ensuring that health-care decisions are grounded in robust evidence and cost–effectiveness. HTAs support transparent and rational resource allocation, helping to prioritize innovative therapies that offer meaningful clinical benefit. Integrating HTA findings into clinical guideline development enhances the credibility, efficiency and sustainability of the health-care system, ultimately improving patient access to high-value care.

## References


1. European Union. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Off J Eur Union 2021;L458/1:1–32 (http://data.europa.eu/eli/reg/2021/2282/oj).
2. Chantzaras A, Margetis A, Kani C, Koutsiouris V, Bacopoulou F. Health technology assessment of medicinal products in Greece: a 5-year (2018–2023) review of timelines and productivity. Int J Technol Assess Health Care. 2024;40(1):e40 (https://doi.org/10.1017/S0266462324000485).
3. The health technology assessment landscape in Greece: situation analysis and alignment with the European Union Regulation on health technology assessment. Copenhagen: WHO Regional Office for Europe; [in press].
4. Littlejohns P, Sharma T, Jeong K. Social values and health priority setting in England: "values" based decision making. J Health Org Manag. 2012;26(3):363–71 (https://doi.org/10.1108/14777261211239007).
5. Clark S, Weale A. Social values in health priority setting: a conceptual framework. J Health Org Manag. 2012;26(3):293–316 (https://doi.org/10.1108/14777261211238954).
6. The GRADE working group [website]. The GRADE Working Group; 2025 (https://www.gradeworkinggroup.org/).
7. Parmelli E, Amato L, Oxman AD, Alonso-Coello P, Brunetti M, Moberg J et al. GRADE Evidence to Decision (EtD) framework for coverage decisions. Int J Technol Assess Health Care. 2017;33(2):176–82 (https://doi.org/10.1017/S0266462317000447).
8. European Union. Directive 2004/109/EC of the European Parliament and of the Council of 15 December 2004 on the harmonisation of transparency requirements in relation to information about issuers whose securities are admitted to trading on a regulated market and amending Directive 2001/34/EC. Off J Eur Union 2024;L390:38–57 (https://eur-lex.europa.eu/eli/dir/2004/109/oj/eng).
9. WHO/Europe Access to Novel Medicines Platform [website]. WHO Regional Office for Europe; 2025 (https://www.who.int/europe/initiatives/who-europe-access-to-novel-medicines-platform).

## Annex 1. PICO questionnaire to be completed by Health Technology Developer

# Initial PICO proposal

## Trade name

**Indication included in the European Medicines Agency Committee for Medicinal Products for Human Use positive opinion**

**Therapeutic indication requested for evaluation**

**Epidemiology and social importance of the disease**

**Instructions for the therapeutic framework in the context of epidemiology and social importance of the disease**

**Epidemiology**

Briefly describe the disease for which the drug is indicated for therapy. Describe the epidemiology (prevalence and incidence data) and number of patients in Greece, explaining the rationale for assigning the number of patients to the indication(s) under evaluation.

**Social importance of the disease**

Clearly describe the impact of the disease on society (burden of the disease). At this point, ethical and societal facts associated with the group of patients under analysis can be considered, including impact on patients' quality of life, mortality and clinical-demographic characteristics of patients.

Support information with objective and specific indicators that quantitatively inform the expression "burden of disease" and impacts measured qualitatively or quantitatively by the use of technology.

**Description of the medicine and available alternatives**

**Instructions for therapeutic framing in the context of the description of the medicinal product and available alternatives**

Provide general information about the drug, mechanism of action, positioning in the therapeutic arsenal of the disease and information on whether it fills a therapeutic gap, as considered relevant in this evaluation.

Describe current therapeutic options for the disease in question.

Confirm that all the presentations submitted in the funding application comply with the dosage stipulated in the Summary of Product Characteristics and the sizing agreed.

**Instruction for the selection of the comparator (according to the approved methodology):**

The selected comparator or reference alternative must cumulatively comply with the following requirements:

- Be used habitually in clinical practice;
- Be validated for the respective indication/population by scientific evidence in relation to its efficacy and safety;
- When the comparator is a drug, the dosage and the interval of administration must be in accordance with the SmPC;
- Have already decided to finance, marketed and with reported consumption;

**Comparators by indication/subpopulation**

| | **Indication /subpopulation** | **Intervention** | **Comparator**(s) – both individual and combination therapies | **Justification for** |
|---|---|---|---|---|
| ***1*** | | | | |
| ***2*** | | | | |
| ***3*** | | | | |

**Comparative measures of effectiveness and safety**

**Instruction for the classification of outcomes (according to the approved methodology)**

It is recommended that outcomes are classified as critical and non-critical, as referenced in the approved evaluation methodology. The outcome should be considered critical by the evaluator when it influences the direction of the evaluation (for details, see bibliography: 12. "GRADE guidelines: 11. *Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes" – Gordon Guyatt et al.* Vol. 66, Issue 2, p151–157; Published online: April 30 2012).

| **Evaluation measures** | **Score*** | **Classification of the importance of the measures*** |
|---|---|---|
| ***Measures of effectiveness*** | | |
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| ***Safety measures*** | | |
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*According to the GRADE methodology, outcomes should be quantified on a scale of 1–9 to rank their importance. Outcomes classified as important should be given a score between 4 and 6; outcomes classified as critical should be given a score between 7 and 9 (https://doi.org/10.1016/j.jclinepi.2010.09.012).

## References


1. Include references used, particularly, in epidemiology
2. …
3. …
4.


## Date

## Annex 2. Template for clinical assessment dossier submission

For the clinical assessment use the following for the submission:

https://health.ec.europa.eu/document/download/ed47ebff-5f37-4861-bcf9-5af5a92e08bc_en?filename=hta_jca_mp_dossier-template_tables_en.docx

## Annex 3. Template for tables submission for the clinical dossier submission

For the clinical assessment use the following for the clinical assessment tables submission:

https://health.ec.europa.eu/document/download/4c99b092-1dad-4623-a5bb-ee9631022ef9_en?filename=hta_jca_mp_dossier-template_annex1_en.docx

# Annex 4. Template for "Economic assessment and other considerations" dossier submission

Appendix A.

#### A.1.1 Modelling of efficacy in the health economic analysis

If a cost-comparison or a minimization analysis is performed, parts of this section may not be relevant to complete. Please write “not applicable” in such cases.

#### A.1.2 Presentation of efficacy data from the clinical documentation used in the model

Please describe how efficacy has been modelled in the health economic analysis. This includes extrapolation of efficacy data and calculation of transition probabilities (for a Markov model) and a description of any other model assumptions related to efficacy. The clinical data, which are the basis for modelling of the effect in the health economic analysis, must basically come from the same data cut as the clinical data and results presented in Annex 2 and Annex 3. If the efficacy data are considered mature, and extrapolation was deemed unnecessary, please state how the efficacy data were applied in the model.

##### A.1.2.1 Extrapolation of efficacy data

Please present the main assumptions and methods used for extrapolating data. The full methodology description and results must be presented. If extrapolations are not of relevance for this application, please write “not applicable”.

##### A.1.2.2 Calculation of transition probabilities

If transition probabilities that were calculated from clinical data have been used, they must also be presented. Please demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe how the clinical outcomes have been transformed, including any other relevant details here.

Include a figure showing the proportion of patients in each health state per cycle in a stacked plot if a Markov model has been used, and present the transition probabilities. If there is evidence suggesting that transition probabilities may change over time, the level of integration of this change must be clearly stated in the analysis. If there is evidence that this is the case but it has not been included, provide an explanation of why it has not been included. Describe the relevance of the selected estimates for Greek clinical practice.

##### A.1.2.3 Presentation of efficacy data from additional documentation

If efficacy data from additional documentation are applied in the health economic model, please fill in this section accordingly.

##### A.1.2.4 Modelling effects of subsequent treatments

Please describe how the clinical effects of potential subsequent treatments are modelled, if subsequent treatment lines differ between intervention and comparator. This includes a

description of which references have been used to justify the assumptions – for example, data from registrational trial, external studies, clinical databases or real-world evidence.

#### A.1.2.5 Other assumptions regarding efficacy in the model

Please state and justify all assumptions regarding efficacy not previously described in the model.

#### A.1.2.6 Overview of modelled average treatment length and time in model health state

Please present estimates for the modelled average and modelled median of the effect measures predicted by the extrapolation model. The estimates must not have been modified with discounting and half-cycle correction. However, the estimate must be adjusted for background mortality of the Greek population (if relevant).

### A.1.3 Safety

The application must contain safety data from the same studies and reports used to document the efficacy of the intervention and the comparator. In cases where safety data are available for a population that is considerably larger than the population in the studies of clinical efficacy, these data must also be submitted (in separate tables).

The terms used to describe safety must be clearly defined – such as adverse events (all causes/regardless of attribution) and adverse reactions (treatment-related adverse events).

In cases where safety data are not available for the intervention and/or comparator, please instead submit data that are as far as possible equivalent to the data requested below.

#### A.1.3.1 Safety data from the clinical documentation

Please state the definition of the safety population. Clearly state the source of the data and the time period the data cover/median treatment duration for all evidence. Describe how safety data are used in the health economic model. The applicant must justify any exclusion of relevant safety data in the health economic analysis.

#### A.1.3.2 Safety data from external literature applied in the health economic model

If safety data from external literature were used in the health economic analysis, please describe how they were applied in the model. Please list the adverse events applied in the model.

### A.1.4 Documentation of health-related quality of life

If a cost-utility analysis is performed, the focus must be on comparing the intervention and the comparator's effect on health-related quality of life measured in the clinical studies. If a cost-minimization analysis is carried out, please write "not applicable".

In general, health-related quality of life should be based on the five-level generic measuring instrument EQ-5D-5L created by the EuroQol Group[2] to make comparison between different assessments possible. In cases where health-related quality of life data based on EQ-5D-5L are not available, other generic or disease-specific instruments must be included and mapped to EQ-5D-5L, with validated mapping algorithms if possible. If the studies included have collected health-related quality of life data with disease-specific instruments in addition to EQ-5D-5L or other generic measuring instruments, these can be reported as supplementary information. The reason for their inclusion in the assessment must be well argued.

#### A.1.4.1 Presentation of health-related quality of life data

If data from multiple health-related quality of life instruments are included, please fill out section details and results for each instrument. Please describe and justify the choice of study design – including, but not limited to:

- the a priori expectations of changes in health-related quality of life and the clinical rationale for the changes;
- reasons for choosing the instrument used to measure health-related quality of life (validity, reliability and sensitivity with regard to patient population);
- whether the instrument was used in the manner for which it is validated;
- whether the study design or chosen instrument caused a risk of bias; and
- whether the population contributing to health-related quality of life data differs from the population contributing to other clinical outcome data, describing the differences and their consequences for the assessment.

Please describe and justify the data collection in terms of:

- how and at which time points the health-related quality of life data were collected;
- relevant data collection time points;
- any missing observations;
- each timepoint for which the number and percentage are missing since randomization;
- each timepoint for which the number and percentage are completed (defining the completion rate as the percentage completed by patients “at risk” at time point “x”);
- how missing observations were handled and what assumptions were made;
- the characteristics of patients with missing values, comparing their characteristics to the population without missing values; and
- health-related quality of life results.

Provide results at baseline and at all relevant data collection timepoints in the health-related quality of life instrument. Argue for the relevance of the selected data collection timepoints.

Include a graph displaying the mean change (with error bars showing the 95% confidence intervals) from baseline through the different data collection time points for both the intervention and comparator.

#### A.1.4.2 Health state utility values used in the health economic model

[2] https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/

If studies other than the study forming the basis for clinical effectiveness have been applied for health state utility values, please provide the information. Describe any mapping methods if applied.

- Describe the purpose of the original mapping study: thoroughly describe the study and patient characteristics on which the mapping is based, and compare it to the patient population included in the application.
- Briefly describe the methods for choosing the patient population, recruiting patients and data collection in the mapping study, including the number of patients and censored patients, if any.
- Describe the statistical methods used for estimating the overlap between the two questionnaires in the mapping study, including choice of statistical tests and statistical models for the mapping algorithm.
- Present the performance of the statistical models tested and the reasoning for choosing the model used to estimate the final mapping algorithm.
- Present the uncertainty of the utility values estimated through the mapping, and how said uncertainty was calculated.
- Describe the preference weights relevant to the mapping, and how they were applied in the actual mapping.

#### A.1.4.3 Disutility calculation

If disutilities associated with adverse events are applied in the health economic model, complete the following and list the disutilities. Justify why disutilities are relevant to include and to what extent the inclusion captures relevant adverse events. Describe how disutilities are calculated and include a formula presenting the calculation.

#### A.1.4.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

If studies other than the study forming the basis for relative efficacy have been used for health state utility values, please add the information. All other studies must be identified in a systematic literature review, and described.

### A.1.5 Resource use and associated costs

Please describe the resource use and associated costs. If unit costs have been included in the model using diagnosis-related group tariffs, provide a description of the diagnosis and procedure codes that have been used to find the diagnosis-related group code in Greece. State the basis for all assumed costs, along with a reference. Include medicinal product information used in the model for the cost calculations (intervention and comparator) in the health economic analysis, including assumptions concerning the treatment duration for the intervention and the comparator. If time-on-treatment data are used to extrapolate the treatment duration, please describe the method used. Some treatments require co-administration – for example, of prophylactics to minimize the risk of experiencing adverse events. If this is the case for the comparator and/or the new intervention, the medicine costs of the co-administrations must be included in the analysis. Describe the rationale for including or not including disease management costs associated with the intervention and

comparator. Describe how the costs of adverse events have been modelled. Describe assumptions concerning the following topics:

- the proportion of patients estimated to be treated with subsequent treatment;
- if relevant, the distribution/share of subsequent therapies in cases where more than one subsequent treatment is available for the patient population;
- the dosing schedule description and route of administration;
- relative dose intensity;
- medicine waste;
- if relevant, resource use and costs associated with administration, monitoring and management of adverse events; and
- average duration of treatment.

The costs incurred by patients and their families as a consequence of the medicine treatment (transport costs and time spent) must be included, if relevant, separately.

### A.1.6 Results

If a cost-minimization analysis is performed, parts of this section may not be relevant to complete. Please write "not applicable" in such cases, and provide an overview of the base case or standard analysis, including the central aspects of the model parameters. Summarize the results for the intervention and comparator for all costs and quality-adjusted life-years, and calculate the incremental cost–effectiveness ratio.

#### A.1.6.1 Sensitivity analyses

Please present the results obtained from deterministic sensitivity analyses and the probabilistic sensitivity analysis. Where relevant and if of interest, the value of information – including the expected value of perfect information analysis – can be also included.

### A.1.7 Budget impact analysis

The budget impact analysis for five years should be submitted here, including assumptions about the estimated number of patients to be treated over the next five-year period if the medicine is introduced, adjusting for market share as appropriate or not recommended, and implications on the estimated budget accordingly.

**Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | **Recommendation** | | | | |
| [Name of intervention] | | | | | |
| [Name of comparator] | | | | | |
| | **Non-recommendation** | | | | |

| | | | | | |
|---|---|---|---|---|---|
| [Name of intervention] | | | | | |
| [Name of comparator] | | | | | |

**Expected budget impact of recommending the medicine for the indication**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **The medicine under consideration is recommended** | | | | | |
| **The medicine under consideration is NOT recommended** | | | | | |
| Budget impact of the recommendation | | | | | |

### A.1.8 Other considerations

Please present the results for the other considerations domains of ethical, legal, social, feasibility and organizational aspects of the medicinal product.

## Annex 5. Template for clinical expert input

# CLINICAL EXPERT INPUT TEMPLATE

National Health Technology Assessment

| EVALUATION DATA | |
|---|---|
| **Pharmaceutical product – trade name** | |
| **Active substance** | |
| **Pharmaceutical form/route of administration** | |
| **Indication** | |



### Brief instructions to participants

This questionnaire aims to collect the evidence-based **clinical opinion and experience** of individual physicians on the **medicinal product under evaluation**, in the context of the national Health Technology Assessment (HTA) process.
Your answers will be used to **synthesize and interpret clinical data** and to better understand the **practical clinical value** of medicine in everyday medical practice.

**How to complete the questionnaire**

The responses are expected to reflect:

- your **personal clinical experience**, and/or
- your knowledge of the scientific literature and established clinical practice.
- Most questions are **open-ended**. You are not required to answer all the individual aspects of each question; please focus on what you consider **clinically relevant and relevant**.
- The questionnaire **does not aim** to redefine the assessment framework (e.g. population, comparators, endpoints), but to collect clinical **judgment and interpretation** of available data.
- Where appropriate, you can highlight:
    - differentiations between patient subgroups,
    - issues of application in daily practice,
    - limitations or uncertainties that you consider clinically significant.

**Practical clarifications**

- Please use **clear, precise and professional wording**.

- If you do not have experience or sufficient knowledge of a query, you can mention it explicitly.
- Citations are not required unless you consider it necessary to understand your answer.

## MODULE 1 – Professional profile and clinical experience

| QUESTION 1.1 | ANSWER |
|---|---|
| **What is your specialty and your professional field?** | **Specialty:**<br>**.....**<br><br>**Sub-specialty or special subject (if any):**<br>**.....** |
| **QUESTION 1.2** | **ANSWER** |
| **How many years of clinical experience do you have in this disease or indication?** | ☐ < 5 years<br>☐ 5–10 years<br>☐ > 10 years |
| **QUESTION 1.3** | **ANSWER** |
| **Approximately how many patients with this indication do you monitor or treat annually in your clinical practice?** | ☐ 1–10<br>☐ 11–50<br>☐ 51–100<br>☐ >100<br>☐ I can't rate |
| **QUESTION 1.4** | **ANSWER** |
| **In what context do you mainly carry out your clinical work?** | ☐ Public sector<br>☐ Private<br>☐ sector Public and private sector<br>☐ Other (please specify):<br>..... |

| QUESTION 1.5 | ANSWER |
|---|---|
| **What is your experience with the medicinal product under evaluation in this indication?** | ☐ Direct and extensive clinical experience<br>☐ Limited direct clinical experience<br>☐ No direct experience, but with experience with drugs of the same therapeutic class<br>☐ No direct clinical experience |

## MODULE 2 – Coverage of clinical needs and practically significant differences

| QUESTION 2.1 | ANSWER |
|---|---|
| **To what extent do the currently available treatment options meet the clinical needs of patients in this particular indication, in daily clinical practice?** | |
| **Short guideline:** You can refer, if relevant, to the main therapeutic objectives in the specific disease and indicate which needs are adequately met and which remain partially or unmet (e.g. symptom control, functionality, quality of life, tolerability/safety, duration of benefit, compliance). | |

| QUESTION 2.2 | ANSWER |
|---|---|
| **What differences between the available treatment options matter most in day-to-day clinical practice, especially in relation to the clinical needs of patients?** | |
| **Short guideline:** You may refer to, but is not limited to, differences in clinically meaningful efficacy, safety/tolerability, mode or frequency of administration, follow-up needs, or overall burden on the patient or system of care. | |

## SECTION 3 – Clinical interpretation of efficacy and safety and uncertainties

| QUESTION 3.1 | ANSWER |
|---|---|
| **How are the clinical efficacy results of the medicinal product under evaluation interpreted in daily clinical practice and what do they mean in practice for the patient?** | |
| **Short instruction:** The question concerns the clinical significance of the effectiveness of the drug in practice (e.g. control of the disease, improvement of symptoms or functionality) and not the detailed presentation of clinical studies. | |

| QUESTION 3.2 | ANSWER |
|---|---|

| | |
|---|---|
| **What characteristics of the efficacy of the medicinal product under evaluation do you consider to be of essential clinical importance for the patient in everyday practice?** | |
| **Short instruction:** You can refer, but is not limited to, the magnitude of the improvement, its duration or stability, the timing of the onset of the result or the extent to which it affects daily life, functionality or the need for further interventions. | |

| QUESTION 3.3 | ANSWER |
|---|---|
| **What safety issues of the medicinal product under evaluation are highlighted in clinical practice and what is their practical significance for its use?** | |
| **Short Guideline:** You can refer to side effects or other risks that affect patient management, the need for follow-up, treatment adjustments, or continuation/discontinuation of treatment. | |

| QUESTION 3.4 | ANSWER |
|---|---|
| **What limitations or uncertainties of the medicinal product under evaluation should be taken into account when interpreting clinical results and using it in practice?** | |
| **Brief Guideline:** You may refer, but is not limited to, issues related to the duration or durability of the benefit, specific patient subgroups, limited long-term use experience, or other factors that may affect clinical application. | |

## UNIT 4 – Position of the drug in the treatment sequence

| QUESTION 4.1 | ANSWER |
|---|---|
| **In your opinion, how does the medicinal product under evaluation fit into the therapeutic sequence of this indication in clinical practice?** | |
| **Short instruction:** You can refer, if relevant, to the location of the medicine in relation to existing treatment options (e.g. treatment line, alternative or complementary use). | |

| QUESTION 4.2 | ANSWER |
|---|---|
| **Which categories or subgroups of patients do you consider to be most appropriate for treatment with the medicinal product under review?** | |
| **QUESTION 4.3** | **ANSWER** |
| **Are there any categories or subgroups of patients for which you consider the medicinal product under evaluation to be less suitable or not indicated in practice?** | |
| **Short Guideline:** Responses may be based on clinical characteristics, such as severity or stage of the disease, previous treatments, comorbidities, biological or other clinical features, uncertainties/limitations, as well as practical factors affecting the administration or follow-up of treatment. | |

## SECTION 5 – Clinical criteria for response and discontinuation of treatment

| QUESTION 5.1 | ANSWER |
|---|---|
| **What clinical criteria are used in practice to assess a patient's response to the medicinal product under evaluation and at what point in time or stage of treatment do you consider this assessment to be clinically reasonable?** | |
| **QUESTION 5.2** | **ANSWER** |
| **What factors or criteria should, in clinical practice, lead to discontinuation of treatment with the medicinal product under evaluation?** | |
| **Short guideline:** Responses may be based on clinical markers, symptomatic or functional criteria, follow-up findings, safety issues, or lack of clinically meaningful benefit, as assessed in daily clinical practice. | |

## MODULE 6 – Application in clinical practice

| QUESTION 6.1 | ANSWER |
|---|---|
| **What conditions do you consider necessary for the correct and safe use of the medicinal product under evaluation in clinical practice?** | |
| **Brief instruction:** You can refer, but is not limited to, issues such as appropriate patient selection, follow-up requirements, clinician experience, the need for special tests or infrastructure, as well as other factors that ensure the safe and proper use of the drug. | |

| QUESTION 6.2 | ANSWER |
|---|---|
| **Are there clinical, organisational or practical barriers that could hinder the widespread application of the medicinal product under evaluation in practice?** | |
| **Short guideline:** Where relevant, you can refer to constraints related to the organisation of health services, the availability of resources, the need for training, the monitoring burden or other factors that may affect the application of the medicine on a large scale. | |

## SECTION 7 – Additional information

| QUESTION 7.1 | ANSWER |
|---|---|
| **Are there any additional clinical observations or remarks that you consider important that have not been covered by the previous questions?** | |
| **Short guideline:** This question allows you to mention anything you consider essential to understanding the clinical use, practical value or limitations of the medicinal product under review, even if it does not fit into any of the previous topics. | |

## SECTION 8 – Summary

| QUESTION 8.1 | ANSWER |
|---|---|
| **Please summarise in up to ten (10) short points the key** | • <br> • |

| | |
|---|---|
| **messages of your clinical opinion regarding the use of the medicinal product under evaluation in this indication.** | • |
| **Brief Instruction:** The summary should capture the most critical conclusions of your clinical view, as they emerge from the previous answers, without extensive analysis or repetition of details. | |

## SECTION 9 – Specific questions

| QUESTION 9.1 | ANSWER |
|---|---|
| **Please answer the specific questions listed below that have been asked by the Clinical Assessment team in the context of this assessment:** | |
| **9.1a** | |
| | |
| **Short instruction:** This section is used to formulate targeted questions that address specific issues of the technology under assessment and may vary from case to case. As long as no specific questions have been asked, the section may be left blank. | |

## Statement

**☐ I declare that the answers I have provided to this questionnaire are based solely on my scientific knowledge and clinical experience and reflect my professional opinion on the medicinal product under evaluation in this indication.**

**☐ I declare that I have read and submitted the relevant Conflict of Interest Statement (COI), in accordance with the applicable procedures of the HTA.**

**☐ I am aware that this contribution, as well as the Conflict of Interest Statement (COI), may be posted and/or made public as part of the HTA procedure, in a way that ensures the protection of personal data.**

| SUBMISSION DETAILS | |
|---|---|
| **Name:** | |
| **Tel. Communication:** | |

| | |
|---|---|
| **Contact Email:** | |
| **Date submitted:** | |

**Signature**

## Annex 6. Template for patient expert input

# PATIENT CONTRIBUTION STANDARD

National Health Technology Assessment

| EVALUATION DATA | |
|---|---|
| **Pharmaceutical product – trade name** | |
| **Active substance** | |
| **Pharmaceutical form/route of administration** | |
| **Indication** | |

### Brief instructions to participants

This brochure aims to collect patient **experiences, needs and priorities** in the context of the national Health Technology Assessment (HTA) process.

The form can be completed either by the patient himself or by a caregiver, parent or legal representative. Where reference is made to the term "patient", it means either the respondent himself or the person he represents.

It is recognised that patients, their representatives and caregivers have **unique knowledge** about what it is like to live with a particular disease or condition. Your answers will be used solely to understand the experience and needs of patients.

Please note the following:

- No clinical efficacy assessment, technology comparison, value-added assessment, or cost-effectiveness analysis is requested.
- Not all aspects of every question are expected to be answered. Please focus on what you consider most important based on your experience.
- Where possible, you can report experiences from **different phases or levels of severity** of the disease.
- Please do not mention the names of doctors, hospitals, or other third-party identifiers.
- Where relevant, please specify whether your answers are based on **direct personal experience** or on the **experience of third-party patients or caregivers** with whom you have been in contact.
- The answers are open-ended. If you do not wish or cannot answer a question, you can indicate it.

Your input is particularly important and will be taken into account in the overall evaluation.

## SECTION 1 – Participant status

| QUESTION 1.1 | ANSWER |
|---|---|
| **In what capacity do you fill in this form?** *(Please select one option)* | ☐ Patient (fill in the form for myself)<br>☐ Carer/informal carer<br>☐ Parent or legal guardian<br>☐ Other person acting as the patient's representative (please specify):<br>..... |
| **Short instruction:** Choosing your status helps to correctly interpret the answers that follow. The form can be filled in both by the patient himself and by a person representing him. | |

## MODULE 2 – Relationship with a Patient Organisation

| QUESTION 2.1 | ANSWER |
|---|---|
| **Are you a member of a patient association or organization?** *(Please select one option)* | ☐ Yes<br>☐ No |
| **Quick Guideline:** This question aims to understand the broader context of your experience. | |

**Only if you answered "Yes":**

| QUESTION 2.2a | ANSWER |
|---|---|
| **Please indicate the name of the patient association or organization:** | |
| **QUESTION 2.2b** | **ANSWER** |
| **Which disease or diseases does the body concern?** | |
| **QUESTION 2.2c** | **ANSWER** |
| **Has your patient organisation received, in the last 24 months, any funding from:**<br>• the company that markets the medicinal product under evaluation, and/or<br>• Companies that have medicinal products used as alternative or comparative therapies | ☐ Yes<br>☐ No<br>☐ I don't know |

| | |
|---|---|
| (comparators) for this indication? | |
| **QUESTION 2.2d** | **ANSWER** |
| **Only if you answered "Yes" and if you are aware of it:**<br><br>• Name(s) of company(s):<br>• General purpose of funding (e.g. operational support, educational or information actions): | |
| **Short Guide:** This information is requested for **transparency** purposes only and complements – not replaces – the formal declarations of conflicts of interest provided for in the HTA procedure. | |

## UNIT 3 – Experience with treatments

| **QUESTION 3.1** | **ANSWER** |
|---|---|
| **Have you received the medicinal product under evaluation to date?**<br>*(Please select one option)* | ☐ Yes<br>☐ No<br>☐ I don't know / Not applicable |
| **QUESTION 3.2** | **ANSWER** |
| **Only if you answered "Yes":**<br><br>**Please indicate:**<br>• Approximately how long you are taking or have received it:<br>• In what context (e.g. clinical study, early access programme): | |
| **Short Instruction:** This question helps to interpret the answers that follow. You are not required to know or mention technical or clinical details. | |

| **QUESTION 3.3** | **ANSWER** |
|---|---|
| **Have you previously received other medicinal treatments for the same indication, which are currently used as alternatives or** | ☐ Yes<br>☐ No<br>☐ I don't know / Not applicable |

| | |
|---|---|
| **comparators?**<br>*(Please select one option)* | |
| **QUESTION 3.4** | **ANSWER** |
| **Only if you answered "Yes":**<br>**Please list them briefly** (without comparison or evaluation): | |
| **Short instruction:** No comparison between treatments or evaluation of their effectiveness is requested. The information is used exclusively to understand the treatment history. | |

## SECTION 4 – Information on the disease/condition

| QUESTION 4.1 | ANSWER |
|---|---|
| **To facilitate the correct interpretation of your answers, please provide brief information about the disease or condition.** | |
| **Age group:** | ☐ 0-17 ☐ 18-35 ☐ 36-50 ☐ 51-70 ☐ >70 |
| **Gender:** | ☐ Male ☐ Woman ☐ Other ☐ I do not wish to declare |
| **Disease/Condition:** | |
| **Stage, severity or course of the disease:** | |
| **Therapeutic history:**<br>*(indicatively: how the diagnosis was made, what treatments have been taken)* | |
| **Any additional information you find useful for understanding your experience:** | |
| **Quick Guide:** This information is used solely for Health Technology Assessment (HTA) purposes and is processed in accordance with the General Data Protection Regulation (GDPR). Any reference to public documents will be made in anonymized form. If you do not wish or are unable to respond to a point, you can omit it. | |

## SECTION 5 – Effects of the disease

| QUESTION 5.1 | ANSWER |
|---|---|

| | |
|---|---|
| **How does the disease or condition affect your daily life?**<br>*(Please describe the effects as you experience them.)*<br>You may, if you wish, refer to:<br>• symptoms and physical burden,<br>• functionality and autonomy;<br>• work, education or daily activities;<br>• psychological or social impacts. | |
| **Quick Guideline:** No medical jargon is required. Please focus on what matters most to you in everyday life. | |

| QUESTION 5.2 | ANSWER |
|---|---|
| **If there is a caregiver, how does the disease or condition affect his/her life?**<br>*(e.g. burden, work, family life, organisational or financial difficulties)* | ☐ There is no caregiver |
| **Short instruction:** This question is about the carers' experience where relevant. If there is no caregiver or you do not wish to answer, you can state it. | |

## MODULE 6 – Experience with available treatments

| QUESTION 6.1 | ANSWER |
|---|---|
| **To what extent do the treatments available today meet your needs in practice?**<br>*(Please reply based on your experience.)*<br>You may, if you wish, refer to:<br>• whether the symptoms are being treated satisfactorily; | |

| | |
|---|---|
| • side effects or difficulties you have experienced;<br>• the way and frequency of administration and how they affect daily life,<br>• the practical burden or difficulty of consistency in treatment. | ☐ No treatments available |
| **Short instruction:** No comparison between treatments or evaluation of clinical effectiveness is requested. The question is exclusively about your experience of using the available treatments in everyday life. | |

## SECTION 7 – Patient subgroups

| QUESTION 7.1 | ANSWER |
|---|---|
| **Are there patient groups for whom disease or care involves a greater burden or fewer treatment options?**<br>*(Please reply based on your experience.)*<br>You may, if you wish, refer to:<br>• age groups,<br>• gender,<br>• stage or form of the disease,<br>• coexisting diseases,<br>• place of residence or other factors that you consider important. | |
| **Short Guideline:** This question aims to understand differences in experience and needs between patient groups. No scientific documentation or generalization is required. | |

## SECTION 8 – Priorities and accepted risks

| QUESTION 8.1 | ANSWER |
|---|---|
| **In relation to the specific disease/indication, what do you consider more important than a treatment in practice and what risks do you consider acceptable or unacceptable?** | |

| | |
|---|---|
| *(Please reply based on your priorities and experience.)*<br>You may, if you wish, refer to:<br>• improvement of daily functionality or quality of life,<br>• reduction of symptoms that affect daily life the most,<br>• ease or flexibility in administering treatment,<br>• tolerated or intolerable risks and burdens. | |
| **Short Instruction:** This question aims to understand patients' priorities and choices. There is no right or wrong answer. | |

## SECTION 9 – Perceived advantages and disadvantages

| QUESTION 9.1 | ANSWER |
|---|---|
| **In relation to the specific disease/indication, what do you consider the main advantages of the medicinal product under evaluation from the patient's perspective?**<br>*(Please answer based on your experience or the experience you have observed.)*<br>You may, if you wish, refer to:<br>• changes in daily life or functioning,<br>• relief of symptoms of particular importance;<br>• practical arrangements (e.g. method of administration, frequency);<br>• other positive effects that you consider important. | |
| **Short Instruction:** The question is about perceived experience and not a scientific or clinical evaluation or comparison with other treatments. | |

| QUESTION 9.2 | ANSWER |
|---|---|

| | |
|---|---|
| **In relation to the specific disease/indication, what do you consider to be the main disadvantages or concerns of the medicinal product under evaluation from the patient's perspective?**<br>*(Please answer based on your experience or the experience you have observed.)*<br>You may, if you wish, refer to:<br>• side effects or difficulties you have experienced;<br>• burden on everyday life,<br>• practical difficulties in use;<br>• concerns or limitations that you consider important. | |
| **Short Instruction:** The question is about perceived experience and not a scientific or clinical evaluation or comparison with other treatments. | |

## SECTION 10 – Additional information

| QUESTION 10.1 | ANSWER |
|---|---|
| **Is there any additional information, experience, or observation that you consider important that was not covered in the previous questions?**<br>*(Please reply freely.)* | |
| **Short instruction:** This question gives you the opportunity to mention anything you consider essential to understanding your experience and needs, even if it does not fit into any of the previous topics. | |

## SECTION 11 – Summary

| QUESTION 11.1 | ANSWER |
|---|---|
| **In up to ten (10) short statements, please summarize the most important points of your contribution.** | •<br>•<br>• |

| | |
|---|---|
| *(Focus on what you find most critical to consider.)* | |
| **Brief:** This summary helps to understand the key messages from the patient's perspective. It can include priorities, needs, advantages, or concerns that you find particularly important. | |

## Statement

**☐ I declare that the answers I provided to this questionnaire are based on my personal experience, in accordance with my capacity as stated above, and honestly reflect my views and experiences in relation to the disease and related drug therapy.**

**☐ I declare that I have read and submitted the relevant Conflict of Interest Statement (COI), if required, in accordance with the applicable procedures of the HTA.**

**☐ I am aware that this contribution, as well as any conflict of interest (COI) statement, may be posted and/or made public as part of the HTA process, in a way that ensures the protection of personal data.**

| **SUBMISSION DETAILS** | |
|---|---|
| **Name:** | |
| **Tel. Communication:** | |
| **Contact Email:** | |
| **Date submitted:** | |

**Signature**