Project No. 101045956

Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19

Deliverable 7.1

Overview of policy landscape

Exploring policy issues for health economic evaluation of inpatient medicines

WP 7 – Socio-economic impact and cost effectiveness analyses (HTA)

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Partner short names

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accelCH	accelopment Schweiz AG
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UMCG	Universitair Medisch Centrum Groningen

Abbreviations

AMNOG	Arzneimittelmarkt-Neuordnungsgesetz
ARDS	Acute respiratory distress syndrome
ASMR	Amelioration du Service Medical Rendu
BIA	Budget impact analysis
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus Disease 2019
CUA	Cost-utility analysis
D	Deliverable
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
EQ-5D	EuroQol 5D
HEE	Health economic evaluation
HPF	Hospital pharmaceutical formulary
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICU	Intensive care unit
IL-6	Interleukin-6
ISPOR	International Society for Pharmacoeconomics and Outcomes
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MAH	Marketing authorisation holder
PPRI	Pharmaceutical Pricing and Reimbursement Information
PSA	Probabilistic sensitivity analysis
PTC	Pharmaceutical and therapeutics committee
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SARS	Severe acute respiratory syndrome
SHI	Statutory health insurance
WHO	World Health Organization
WP	Work package

1. Executive Summary

The COVend project aims to deliver a new effective therapy by using the peptide FX06 for the clinical management of COVID-19, including for the prevention of disease progression to severe illness and intensive care unit (ICU) admission. The overarching goal of WP7 of the COVend project is to evaluate FX06 from a health economic perspective. Health economic evaluation (HEE) of new interventions is gaining increased importance worldwide, as decision-makers on reimbursement and implementation are challenged to balance societal affordability with patient access, due to limited resources and expanding healthcare expenditure. The current deliverable is the first in a series of five deliverables and provides an overview of policy issues that would need to be addressed in the health economic analysis.

1.1 Purpose and scope of the deliverable

The deliverable explores relevant policies in the process of reimbursement and payment of new interventions to be used in a hospital setting and identifies differences and similarities across national methodological guidelines for the conduct of HEEs. The scope of the deliverable is narrowed to countries that take part in the clinical study of the COVend project. Furthermore, since FX06 only tends to be used in a hospital setting, the focus was on policies and regulations that apply to pharmaceuticals for inpatient use.

1.2 Outcomes

The report reveals challenges in regulatory procedures as well as differences in the required design of a health economic analysis across the countries considered. Substantial variation was found in the sequence of procedural steps and the assessment criteria used in the reimbursement process. Commonly used criteria, in order of use, are therapeutic benefit, budget impact, cost-effectiveness, medical need and priority, and safety. After reimbursement has been granted on a national level, the actual use and funding of inpatient medicines are in most countries dependent on a positive assessment by individual hospitals. Hospitals assess, among others, the financial impact of the new therapy, which stresses the relevance of a dynamic, hospital-specific budget impact analysis (BIA). In response to the COVID-19 pandemic, several procedures for market access to COVID-19 therapeutics have been adjusted. However, these may become ineffective over time, depending on the emergency phase of the pandemic.

Despite relatively high comparability across guidelines on the design of HEE in European countries, substantial differences were found in the choice of the perspective of the analysis and the choice of comparators. Thus, the health economic model needs to be designed in a dynamic way, in which the model structure and its parameters can be easily adjusted. It should be noticed that an emerging EU regulation on joint Health Technology Assessment (HTA) may provide relevant opportunities to reconcile differences in recommendations on the design of HEE. Based on the content of the present report, we plan to design a cost-utility analysis (CUA), complemented by a hospital-specific BIA. The model should ideally include all patient-specific characteristics that are analysed as part of the COVend project.

2. Introduction

The SARS-CoV-2 pandemic has had a tremendous impact on humanity since cases were first reported in China in late 2019. As of July 1st, 2022, a total of 543 million confirmed cases of COVID-19, including 6.3 million deaths, have been reported worldwide [1]. Despite general prevention measures and the administering of over 10 billion vaccine doses, numbers of confirmed cases peaked globally since November 2021 with the emergence of the Omicron variant [2]. Thus far, the disease severity of the BA.1 and BA.2 lineages was found to be lower compared to the earlier dominant Delta variant [3, 4]. However, with the emergence of new SARS-CoV-2 variants, increased transmissibility or pathogenicity can result in an increase in hospitalisations, ICU admissions, and deaths.

Patients infected with SARS-CoV-2 can be categorised into three different groups of disease severity: mild or non-severe COVID-19 (with symptoms like fever, cough, headache, muscle pain, loss of taste and smell), severe COVID-19 (oxygen saturation below 90% on room air, signs of pneumonia and signs of severe respiratory distress), and critical COVID-19 (acute respiratory distress syndrome -ARDS-, septic shock, and/or multiple organ dysfunction) [5].

2.1 Current treatment options

Due to the need to overcome the pandemic and to address the unmet medical need, many potential therapeutical agents have been studied globally, including corticosteroids, immunomodulatory agents, and antivirals [6]. By now, several agents had been approved by the European Medicines Agency (EMA) to treat patients with COVID-19. These treatment options can be subdivided into i. antiviral drugs (Remdesivir/Veklury®, Ritonavir- Nirmatrelvir/Paxlovid®), ii. anti-inflammatory drugs (Anakinra/Kineret®), and iii. monoclonal antibodies (Casirivimab-Imdevimab/Ronapreve™ also known as REGEN-COV™, Sotrovimab/Xevudy®, Regdanvimab/Regkirona®, Tixagevimab-Cilgavimab/Evusheld® and Tocilizumab/RoActemra®) [7].

Despite balanced benefit-risk assessments based on randomised controlled trials (RCTs), treatment outcome may be affected by a number of factors. One factor is the clinical efficacy and availability of a treatment option at the current disease stage. Disease severity appears to be driven not only by the virus response (i.e. the replication of the virus), but also by the host response (i.e. a dysregulated immune response) [8, 9]. Antivirals target the viral entry and are ultimately used in an early stage of the disease, whereas anti-inflammatories target the host response in a later stage. Furthermore, since infectious organisms can mutate over time, antivirals and monoclonal antibodies may lose their efficacy against certain variants. Regdanvimab for instance retained no inhibitory activity to the Omicron variant [10]. Moreover, all EMA-approved medications thus far need to be administered parenteral, except for the oral drug Paxlovid®. One major concern of Paxlovid®, however, is its complex drug-drug interaction potential [11]. Another promising option in the treatment of severe COVID-19 is the glucocorticoid dexamethasone. In an RCT, dexamethasone reduced mortality by one-third in patients who received respiratory support [12]. However, the incidence of serious adverse events was not reduced. Overall, an efficient causal therapy that reliably can prevent progression of patients with mild or moderate COVID-19 is still lacking.

2.2 FX06 in the treatment of COVID-19

An essential contributor to the pathophysiology of SARS-CoV-2 is the endothelium. Evidence suggests that endothelial cells are both a critical target of SARS-CoV-2 and an effector contributing to a pro-

inflammatory and procoagulatory state. The two latter lead to severe complications like capillary leakage and pulmonary edema [13-15]. Therefore, the protection of the endothelium could be an effective treatment to prevent COVID-19-infected patients from disease progression.

An effective therapy against COVID-19-induced endothelial damage may be the use of FX06, a peptide naturally occurring in the human blood in picomolar concentrations. FX06 is known for its immunomodulatory properties and turned out to preserve the endothelial barrier [16, 17]. An observational case series with FX06 and patients suffering COVID-19-associated ARDS showed increased oxygenation levels, indicating a normalisation of the pulmonary vasculature, and decreased levels of interleukin-6 (IL-6, one out of several pro-inflammatory cytokines released as a consequence of severe COVID-19) [18].

The COVend project aims to assess the efficacy of FX06 for the clinical management of COVID-19, including for the prevention of disease progression to severe illness and hospitalisation. As of autumn 2022, the first hospitalised, non-intubated patients with moderate symptoms of COVID-19 will be included in a placebo-controlled, multi-national phase II/III study, named IXION. One specific objective of COVend is to evaluate FX06 from a health economic perspective, which is an essential part of HTA.

2.3 Health Technology Assessment

HTA is a widely used multidisciplinary process that uses explicit methods to determine clinical benefits (i.e. efficacy, effectiveness and safety) as well as social, economic, organisational and ethical aspects of a health technology. Due to limited healthcare resources and ever-increasing healthcare costs globally, policy-makers are challenged to balance societal affordability with patient access. Therefore, deciding on whether to adopt a medical innovation needs to be based on a holistic approach of properties, effects, and/or impacts of a new intervention. HTA aims to support decision-making on determining the relative value for money provided by the new intervention compared to one or more existing alternatives. Even in the phase of clinical research, early assessment of the health technology in question can be applied to foster a reimbursement decision and widespread use [19].

2.4 Aim and structure of the report

Prior to the conduct of economic evaluation, it is important to identify any specific hurdles or demands from an economic perspective, as well as any barriers and facilitators that could affect the implementation of FX06. The first part of this exploratory research goal is captured by the current deliverable; the barrier and facilitator analysis will be conducted as part of a subsequent deliverable (D7.2). The present report's objective is twofold: (I) to provide an overview of reimbursement and payment policies applied for medicines used in a hospital setting in each of the participating countries of the project, and (II) to identify differences in key recommendations for HEE in these countries. The report's output could reveal challenges in regulatory procedures as well as differences in the required design of HEEs that need to be addressed in the multi-country analysis of WP7.

This chapter is succeeded by a brief description of the methods used to collect relevant data on the subject (Chapter 3). Chapter 4 describes the regulatory process of reimbursement and payment and highlights relevant country-specific practices used today by health authorities and governments. Chapter 5 summarises the similarities and differences in technical recommendations and guidance for HEE across the countries considered. Chapter 6 elaborates on recommendations and future actions for WP7.

3. Methods

3.1 Scope

The scope of the report is narrowed to countries that take part in the clinical study of the COVend project. These include France, Germany, Italy, Lithuania, The Netherlands, Portugal, Romania, and Spain (see Figure 1). Furthermore, since FX06 only tends to be used in a hospital setting, the focus of the report was on policies and regulations that apply to pharmaceuticals for inpatient use, where applicable. The distinction between outpatient and inpatient care is not always clear though, as hospitals throughout Europe deliver outpatient care as well (e.g. hospital pharmacies). Moreover, not every national health system is reporting on basis of the mode of provision of care (i.e. inpatient, day-care, home-based care, outpatient) [20]. Since the objective of the report was to provide a general overview of reimbursement and payment policies for inpatient medicines, an exact definition of inpatient pharmaceuticals was left aside.

Figure 1 *Graphical representation of the eight countries considered in the report.*

3.2 Collection of documents

We searched for both scientific literature as well as grey literature related to reimbursement and payment policies that are valid in the aforementioned countries. Grey literature included legislative documents at a European level, reports commissioned by the World Health Organization (WHO), policy briefs and working papers of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network, national regulatory documents such as governmental regulations on the reimbursement process, and guidelines of HTA agencies. To obtain more details and data, manual searches were performed using the reference lists of key publications.

To structure and support the descriptive analysis of guidelines for HEEs, a tool entitled “Pharmacoeconomic Guidelines Around The World” of the International Society for Pharmacoeconomics and Outcomes (ISPOR) was used [21]. The tool provides a comparative table with key features for most of the countries in scope. The content of the ISPOR tool was updated with renewed publications of HEE guidelines and supplemented with findings from recent scientific reviews on cross-country comparisons of HEE guidelines.

4. Reimbursement and payment policies for inpatient medicines

The process of market access of pharmaceuticals entails various activities, which can be subdivided into pre-launch, peri-launch, and post-launch activities. Pre-launch activities are related to initial evidence generation and marketing authorisation and involve policies like horizon scanning and critical drug evaluation. Peri-launch activities include policies for value assessment and pricing and reimbursement tools. Post-launch activities relate to responsible use and include prescription policies and pharmacovigilance [22]. This chapter focuses on the regulatory steps required for the funding of new pharmaceuticals for inpatient use, which mainly fall in the peri-launch class of activities.

4.1 Marketing authorisation

The first regulatory step in the process of market access is marketing authorisation. There are two ways of getting marketing authorisation within the European Union (EU): a national procedure and a centralised procedure. Under the national procedure, the manufacturer applies for authorisation at the Medicines Agency in individual EU Member States, or in several Member States simultaneously via a decentralised procedure or a mutual recognition procedure [23]. In the centralised procedure, which is more common for new, innovative medicines, the application is assessed by the Committee for Medicinal Products for Human Use (CHMP) of the EMA. A positive assessment by the EMA on the medicine's safety, quality, and effectiveness will lead to an advice to the European Commission (EC).

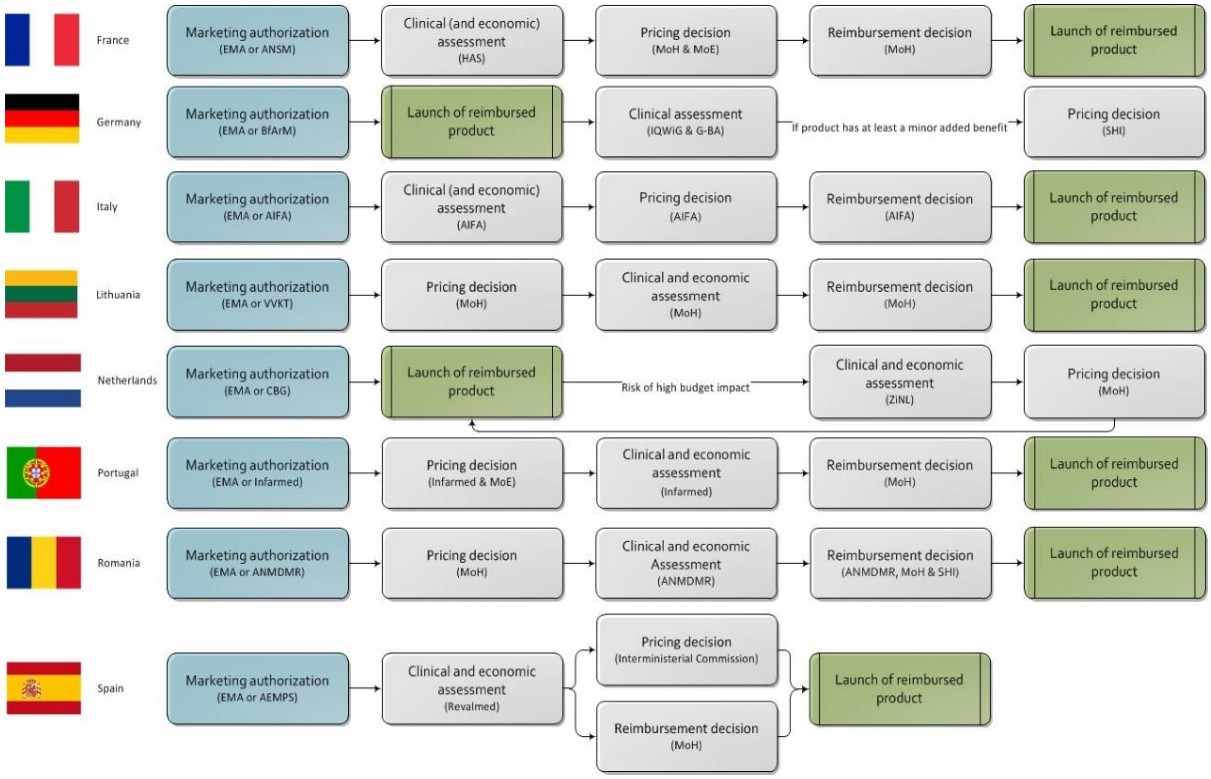

Figure 2 *Simplified overview of regulatory steps in the pricing and reimbursement procedure of medicines for inpatient use until inclusion into the national positive list of the eight countries in scope. Competent authorities are showed between parentheses. Abbreviations: AEMPS = Agencia Española de Medicamentos y Productos Sanitarios, AIFA = Agenzia Italiana del Farmaco, ANMDMR = Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România, ANSM = L'Agence nationale de sécurité du médicament et des produits de santé, BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte, CBG = College ter Beoordeling van Geneesmiddelen, G-BA = Gemeinsamer Bundesausschuss, IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, MoH = Ministry of Health, MoE = Ministry of Economy, SHI = Social Health Insurance, VVKT = Valstybinė Vaistų Kontrolės Tarnyba, ZiNL = Zorginstituut Nederland.*

The EC takes a legally binding decision on market approval, which is then valid in all Member States of the European Economic Area (EEA) at the same time. The centralised route is compulsory for medicines containing new active substances, which are to be used in several types of treatments, including treatments against viral diseases [24]. If the marketing authorisation holder (MAH) considers the medicine to be reimbursed, the process is continued by a decision on the price and reimbursement status of the product (see Figure 2).

4.2 Reimbursement process

Reimbursement decisions are generally made at a national level. Each country has its unique health system characteristics, often shaped by political priorities and economic constraints. Hence, reimbursement processes across countries are far from unified. Despite all types of variations, the tools used to achieve health policy objectives may be similar. The main differences and similarities in reimbursement processes across the countries in scope are described in the following subsections.

4.2.1 Clinical (and economic) assessment

In most countries, the MAH is required to submit a reimbursement application dossier to the competent authority. The dossier should provide clinical and economic evidence of the new medicine and is used as input for HTA. The application is assessed by a dedicated committee as part of the national authority in charge of pricing and reimbursement. An independent expert committee appraises the evaluation and then recommends to the final decision maker on reimbursement of the medicine of concern. The final decision is made by the Ministry of Health or the national Medicines Agency and is subsequently published in the government gazette [25, 26].

According to the EU Transparency Directive, the assessment may not take longer than 90 days from submission date (or 180 days if a price decision is included), unless additional information from the MAH is required [27]. Most jurisdictions require a predetermined ex-factory price to include in the HTA process. However, in France, the medicine price is not included in the assessment, and in Spain, the pricing decision overlaps with the reimbursement decision [25].

Even though all countries in scope use HTA principles in the reimbursement procedure for new medicines, not every country systematically assesses the costs and/or consequences before an authorised hospital medicine can be used in clinical practice. In Germany and the Netherlands, the default for inpatient medicines is reimbursement after marketing authorisation, though some restrictions may apply, mainly for medicines with a high per patient cost or a substantial budget impact. In Germany, the price of a new medicine is not regulated in the first year after market entry (i.e. the price is set by the MAH). However, within three months after product launch, the Institute for Quality and Efficiency in Health Care (IQWiG) performs an early benefit assessment, after which a decision on the added benefit is made by the German Federal Joint Committee (G-BA). A positive benefit assessment is succeeded by price negotiations between the statutory health insurance (SHI) association and the MAH, to determine the reimbursement price after the first year. If no agreement can be made, a cost-benefit analysis may still be considered. This procedure, known as the AMNOG procedure (Act on the Reform of the Market for Medicinal Products), is required for every new pharmaceutical in Germany [28, 29].

In the Netherlands, new pharmaceuticals for inpatient use that meet the ‘established medical science and medical practice’ standards are considered reimbursable [30]. SHI companies and prescribers may

then decide on the reimbursement amount. However, inpatient medicines with disproportionally high costs or a high budget impact (either macro costs of >€40 million/year, or >€50.000/year/patient and macro costs of €10 million/year) may be placed in the so-called 'sluis', meaning they are suspended from reimbursement [31]. The costs and effects of the medicine are then assessed by the Dutch Healthcare Institute (ZiNL), and, in most cases, a positive reimbursement decision can be obtained after successful price negotiations [32]. In 2020, approximately 38% of active substances for which no competition was present were included in the 'sluis' [33].

In the rest of the countries, a reimbursement decision is made after a clinical and/or economic assessment has been performed [25, 34]. In practice, however, the actual use may differ across the countries. Until recently, the assessment procedure has not been fully operationalised in Spain's practice, even though its systematic use is embedded in law [35, 36]. In Romania, the reimbursement decision is based on a scorecard HTA model and a BIA. The scores are based on the efficacy and cost-effectiveness derived from HTA decisions from France, Germany, and the United Kingdom, the reimbursement status in 27 EU countries, and the direct costs of the medicine [34, 37].

4.2.2 Reimbursement eligibility

Across the countries, several aspects are being considered in the reimbursement decision of medicines. The assessment of a new medicine is always started from a clinical point of view, whether or not combined with economic aspects. As shown in Table 1, the added therapeutic benefit is a common criterion for new medicines, while the scientific evidence on additional key criteria like budget impact, cost-effectiveness, medical need, and safety is less consistently assessed [38].

Table 1 *Reimbursement eligibility criteria in clinical and/or economic assessments of medicines for inpatient use per country[a]. Derived from [31, 35, 39-42].*

Country	(Added) therapeutic benefit	Budget impact	Cost-effectiveness	Medical need/ priority	Safety	Others
France[b]	●					●
Italy[c]	●	●	●	●	●	●
Lithuania	●	●	◐	●	●	
Portugal	●	●	●		●	
Romania[d]	●	●	●	●		●
Spain[e]	●	●	●	●		●

a = Germany and The Netherlands are not included in the table. In Germany, none of the listed criteria is of relevance since a medicine is considered reimbursable as soon as it is launched. Early benefit assessments under the AMNOG procedure are focused on the (added) therapeutic benefit though. In the Netherlands, inpatient medicines are only assessed when being placed in the 'sluis'. Assessment criteria are necessity, effectiveness, cost-effectiveness, and feasibility. See also 4.2.1.

b = In France, the criterion is therapeutic benefit but not added therapeutic benefit. The therapeutic benefit which guides the reimbursement decision is based on five criteria: Disease severity, efficacy / tolerance balance, preventive / curative / symptomatic use, therapeutic strategy position and public health interest. Cost-effectiveness is considered for innovative medicines with a significant impact on health expenditures.

c = 'Others' include expected market share and prices in other countries.

d = 'Others' include reimbursement status of the pharmaceutical in other EU Member States. See also 4.2.1.

e = 'Others' include existence of therapeutic alternatives at lower price and degree of innovation of the medicine.

The early benefit assessment as part of the German AMNOG procedure exclusively focuses on the clinical value. Likewise, the reimbursement decision in France is initially based on the therapeutic benefit of the medicine. However, if the MAH deems its product to have a moderate to major added therapeutic benefit (ASMR level I-III) with respect to a defined cost-effectiveness frontier and a significant impact on national health insurance expenditures is anticipated (>€20 million/year), the submission of a cost-effectiveness analysis is required by the French authority [43, 44]. In Italy, the added therapeutic benefit is emphasised as well, as economic benefits are considered after the therapeutic value of the medicine appears to be equal to comparable therapies [45].

4.2.3 Reimbursement status

All countries apply uniform reimbursement rules to medicines. This, however, is less straightforward for countries with strong regional autonomy (Spain, Italy). In these countries, the regions oversee resource allocation, budget decisions, and the procurement of medicines. Although regions have no legal right to deny access to medicines with a national reimbursement status, they can discourage or incentivise use in clinical practice [35, 40].

Once inpatient medicines are deemed reimbursable, the actual use and funding are dependent on their inclusion into a hospital-specific positive list, called a hospital pharmaceutical formulary (HPF). Apart from Romania, HPFs are used in all countries, and are composed and regularly updated by a hospital's Pharmaceutical and Therapeutics Committee (PTC). Though inclusion criteria of HPFs vary per hospital, commonly used criteria are effectiveness, side-effects, and price [26]. The content and use of an HPF may overlap with the national positive list for the outpatient sector. The positive list for the outpatient sector is relevant for the inpatient sector as well in Italy and Spain [40, 41]. In contrast to hospital-specific positive lists, Portugal has a centralised HPF at the national level. Nonetheless, the Portuguese HPF is compiled by PTCs of hospitals [39, 46].

4.3 Payment process

4.3.1 Pricing

During or after the reimbursement application, the manufacturer and the pricing authority negotiate on an ex-factory price. Medicine prices are either controlled by government authorities (price control) or set by the MAH (free pricing). All countries use price control mechanisms for inpatient medicines, although there are substantial differences in scope across countries. Italy, Portugal, Romania, and Spain negotiate ex-factory prices of all reimbursable medicines used in the inpatient sector. France, Lithuania, and The Netherlands control prices of expensive inpatient medicines and apply free pricing for medicines included into Diagnosis-Related Group (DRG) payment. Germany starts negotiating a price after one year of free pricing since market approval. The scope of price regulation mainly depends on the funding mechanism (see 4.3.3).

4.3.2 Procurement

Whereas the negotiated ex-factory price is often made publicly available (not the case for inpatient medicines in Portugal), the actual purchasing price of inpatient medicines is generally kept confidential [25, 47]. For the inpatient sector, where hospitals decide on the actual use of medicines, prices are usually directly negotiated between hospitals and MAHs. The most common pricing policy for hospital medicines is tendering. Other frequently used pricing policies are (public) price negotiations and

conditional pricing via risk-sharing agreements or managed entry agreements for costly medicines [26, 38]. Hospitals may negotiate individually on the purchasing price, although joined or pooled procurement by hospital purchasing groups or regional procurement bodies have gained more interest, as well as centralised procurement at a national or international level [48, 49]. Several international procurement collaborations of medicines exist within Europe, including the BeNeLuxA Initiative on Pharmaceutical Policy (which involves Austria, Belgium, Ireland, Luxembourg, and the Netherlands) and the Valletta Declaration (which mainly involves Mediterranean countries[1]) [50]. The level of procurement particularly depends on the funding mechanism that is being used.

4.3.3 Funding

None of the countries applies direct co-payment for medicines used in an inpatient setting [26]. The expenditure of a new inpatient medicine is generally paid out of the hospital budget. Throughout Europe, public hospitals are mainly remunerated by DRG payment systems [51]. DRGs are financed out of the national or regional budget with a predetermined amount, which is adjusted annually. With a slight modification of an existing DRG, a new medicine and its additional expenditure can be integrated into the lump sum of a DRG [26].

In the case of high-priced or low-volume medicines, the costs might not (directly) be included in DRG payment. Several countries have established extrabudgetary payment systems and specific funds to enable reimbursement for such medicines. For instance, France has a reimbursement list for medicines that fall outside DRG funding, called 'liste en sus'; Germany uses additional charges and NUB (New Methods for Treatment and Screening) payment for new cost-intensive therapies; Italy implemented a €1 billion innovation fund to reimburse new, innovative medicines; and the Netherlands uses 'add-on' payment of expensive medicines that are not included into DRG payment. In general, hospital medicines that are funded by extrabudgetary payments are intended to be included in DRG payment over time [40, 52-54].

4.4 Emerging changes

In response to the unprecedented challenges of the pandemic, some adaptations and reorganisations of reimbursement and payment systems have been proposed and/or implemented.

At national level, several mechanisms exist to respond to emergency situations. In addition to these mechanisms, the European Commission has proposed an EU-strategy on COVID-19 therapeutics [55, 56]. The approach includes the acceleration of regulatory approval, which entails an intensified use of rolling reviews and conditional marketing authorisation, allowing the EMA to assess promising therapeutics before formal application, based on data of ongoing studies. Furthermore, early access to medicines before granted authorisation is stimulated through mechanisms like compassionate-use or emergency-use authorisation. Moreover, in addition to existing voluntary procurement collaborations across Europe (see 4.3.2), new joint procurements of COVID-19 therapeutics by governments are incentivised by the EU-strategy. The strategy likely impacts established systems for pricing, reimbursement, and procurement of COVID-19 therapeutics. However, it should be noted that some efforts may become inactive when the emergency phase of the pandemic is being replaced by a preparedness phase.

[1] Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Cyprus, Slovenia and Croatia

With regard to hospital finances, several countries have adjusted their payment systems to cover additional costs as a consequence of COVID-19-related services and new hygiene requirements, as well as to compensate for the shortfall in hospital revenue due to a lower utilisation of (elective) care [57]. During the first COVID-19 wave in 2020, some countries used the same budget and existing DRGs to cover costs of COVID-19 care, whereas others slightly modified DRG-based payments, adjusted budgets, and even implemented new DRG codes. Depending on the emergency phase of the pandemic it is expected that compensation funds will be phased out over time [58].
Concerning the AMNOG procedure (see 4.2.1), some significant reforms have been proposed by the German federal government, including a reduction of the free pricing period from 12 months to 6 months after product launch. While details and timing of the amendments remain unknown, applicants for reimbursement of new pharmaceuticals should be aware of significant changes and cost-containment measures in the German reimbursement procedure in the near future [59].

4.5 Summary

Regulatory procedures beyond (often centralised) marketing authorisation vary substantially across the countries in scope. Differences can be found in the sequence of procedural steps, as well as in the use of assessment criteria. Overall, in order of use, therapeutic benefit, budget impact, cost-effectiveness, medical need and priority, and safety are the main criteria in the assessment of inpatient medicines in the countries considered. Inpatient medicines are fully reimbursed in all countries considered, meaning direct co-payment is not applicable. After reimbursement has been granted to a new medicine for inpatient use, successful implementation is in many cases dependent on a positive assessment by a hospital's PTC: inclusion into an HPF is pivotal for actual use in clinical practice. Consequently, the costs of newly added inpatient medicines can often be funded out of the defined remuneration of an existing DRG. In response to the COVID-19 pandemic, several regulatory procedures for market access of COVID-19 therapeutics have been accelerated, and close collaboration between competent authorities has gained major importance. However, it should be mentioned that alterations of procedures in response to the COVID-19 pandemic may become ineffective over time, depending on the emergency phase of the current pandemic.

5. Key features of health economic evaluation

To guide pricing and reimbursement of new and existing treatments, all countries in the report's scope use methods and principles of HTA. The assessment and/or evaluation of therapies from a health economic point of view is a cornerstone of HTA. The number of published HEEs has grown globally since decisions on resource allocation increasingly require evidence-based arguments [60].

Many countries have developed guidance on how to design and conduct HEEs, which is used by both applicants for reimbursement and assessors who evaluate the quality of an HEE. Thus far, all countries in the report's scope, except for Romania, have published technical recommendations on HEE [21]. In most cases, technical guidance depends on a country's political and economic context. Consequently, substantial variation can be found across recommendations developed in EU countries. Despite ongoing efforts to harmonise guidance on HEE (for instance, via the European Network for HTA, EUnetHTA), the development of a consolidated technical guideline is still impeded by contextual factors of a country, including research capacity, data availability, and HTA purposes [61, 62].

This chapter summarises the main varieties and commonalities across HEE guidance of the countries in scope. The most impactful variation among key recommendations is described in paragraph 5.1, while common key recommendations are described in paragraph 5.2. Paragraph 5.3 highlights the new regulation on joint HTA across Europe as a relevant change coming into effect soon.

5.1 Varying key recommendations

In general, HEE guidance across the studied countries consists of several key recommendations that are stated explicitly, while other recommendations are provided less straightforward. Some are of mandatory nature, whereas others are recommendatory and provide alternative methods. The main differences among key features are summarised in Table 2 and are described in the following subsections.

Besides a published Spanish guideline on national HTA, a less sophisticated guideline for hospital formularies in Spain has been compiled by the GENESIS group (group for drug evaluation, standardisation and research in drug selection) [63]. The hospital-oriented guidance is considered as well in the analysis, and any diverging recommendations from the Spanish national guideline are considered applicable since FX06 tends to be used in an inpatient setting, and the guideline has been published more recently than the national one.

Table 2 *Key features with major deviation across the countries considered.*

Country (year of publication)	Perspective of analysis	Comparator(s)	Discount rates (costs, effects)	Reference
France (2020)	Collective	All relevant therapies	2.5%, 2.5%	[64]
Germany (2022)	Payer	All relevant therapies	3%, 3%	[65]
Italy (2021)	Payer	Most commonly used	3%, 3%	[66]
Lithuania (2002)	Payer	Most commonly used	5%, 5%	[67]
Netherlands (2016)	Societal	Most commonly used	4%, 1.5%	[68]
Portugal (2019)	Payer	Most efficient alternative	4%, 4%	[69]
Spain* (2010 (2017))	Societal (Payer)	Most commonly used	3%, 3%	[63, 70]

***:** recommendations of the guideline for hospital formularies that diverge from the Spanish national guideline are presented between parentheses.

Perspective. One fundamental methodological aspect of economic evaluation is the perspective of the analysis. The definition and explanation of the perspective will determine the costs and consequences to be included in the analysis. Most guidelines call for a "healthcare perspective" or "payer's perspective", in which the base case analysis considers only the direct (medical and/or nonmedical) costs and health effects that affect only patients. Overall, the healthcare system or government is considered a payer, depending on the healthcare system. For Italy, Portugal, and Spain, the perspective on costs is that of the national health service (NHS). Other countries with an SHI system define healthcare funders as the payer, albeit in different manners. In Germany, for instance, the payer can be defined as the complete SHI system, the SHI branches together, or the community of individuals insured under SHI.

In contrast to a healthcare or payer's perspective, the French guideline prescribes the use of a "collective perspective", which involves all direct costs related to the health intervention, together with health benefits accruing to all individuals. In Spain, the national guideline recommends a "societal perspective", though a payer's perspective is primarily recommended in the hospital-based guideline. The Netherlands recommends a societal perspective as well, in which indirect medical and non-medical costs and health benefits to all individuals should be included in the analysis. Examples of indirect non-medical costs are transportation costs to the healthcare facility and productivity loss resulting from patients' reduced efficiency or inability to work because of morbidity or mortality. Indirect medical costs are future medical costs of remaining alive due to the life-prolonging treatment under assessment. If considered relevant to the research question, a separate inclusion of societal costs is alternatively recommended in all guidelines. The type of costs to be included in the analysis are presented in the table below.

Table 3 *Cost types required to include in the base-case analysis per country.*

Type of costs	Countries
Direct medical costs	All
Direct non-medical costs	France, Germany, Italy, Netherlands, Spain*
Indirect medical costs	Netherlands
Indirect non-medical costs	Netherlands, Spain*

*: only recommended in the Spanish national guideline.

Choice of comparator. The choice of the comparator to which the evaluated intervention is compared, should be the most used one, either as routine clinical practice or in accordance with the standard treatment guidelines. French and German guidelines even state that all relevant treatments in the therapeutic area should be considered as alternatives in the HEE. In France, interventions that are therapeutically relevant, but used to a relatively low extent, and interventions without marketing authorisation, but widely used, should also be considered as comparators. Portugal recommends considering all relevant therapeutic alternatives, after which the comparison can be made with only the most efficient alternative.

Discounting. A further noticeable variation is discounting of future costs and benefits, used in analyses with a time horizon of more than one year. Discount rates vary between 2.5% and 5% and are commonly equal for costs and benefits. This, however, is not the case for the Dutch guideline, which recommends a 4% rate for costs and a 1.5% rate for effects. Recommended discount rates per country are presented in Table 2.

5.2 Common key recommendations

As stated before, some key recommendations are less explicitly formulated. As such, substantial consensus can be perceived among several recommendations. Nevertheless, a clear justification by the analyst for the choices made is often required.

Time horizon. One similarity is the time horizon of the analysis. In most cases, the time horizon is recommended to be based on the natural course of the disease and the expected health effects of the intervention. In general, a lifetime horizon is advocated more or less explicitly. German guidance primarily recommends a time horizon of the average (clinical) study duration, though leaving the option open for an extended secondary time horizon.

Preferred analytical technique. A further less strictly formulated key feature is the preferred analytical technique, which is strongly related to the preferred outcome measure. Most guidelines advocate for the use of quality-adjusted life years (QALYs) to express utility as an outcome measure. Therefore, a CUA is the most preferred type of economic analysis. Italy, Lithuania, and Spain do not explicitly state their preference though.

Preferred utility measure. To measure QALYs, almost all guidelines prefer the EQ-5D (EuroQol 5D) tool, which is a widely used preference-based instrument to measure the health-related quality of life (HRQoL). EQ-5D is generally preferred, though other methods and instruments to assess HRQoL are also recommended, such as the SF-36 (36-Item Short Form Health Survey) instrument, and choice-based valuation methods like Standard Gamble and Time-Trade-Off.

Modeling. All guidelines consider the use of a model-based approach acceptable in HEE. Modeling is especially applicable if trial data is too short for a sufficient analysis, which is often the case. Decision-analytic modeling provides a framework to estimate the cost-effectiveness of an intervention compared to alternative treatments by combining evidence from different sources, rather than using a single study. The type of model chosen (e.g. decision trees, state-transition models, discrete-event simulations, dynamic transmission) is not strictly formulated, though its input values, assumptions, and validity should be described clearly.

Sensitivity analysis. The use of a model-based approach entails that decisions are taken under conditions of uncertainty. To analyse the effect of parameter uncertainty in an HEE, all guidelines recommend (and some even require) to perform both deterministic and probabilistic sensitivity analyses (DSA and PSA). Outputs of PSA include cost-effectiveness planes, cost-effectiveness acceptability curves, and value-of-information analyses [71]. In addition to DSA and PSA, scenario analyses are recommended by most guidelines.

Budget impact analysis. Finally, all countries recommend a BIA to complement the economic evaluation. Both types of analyses have different objectives. In an HEE, the cost and health effects of an intervention are examined, compared to therapeutic alternatives, while a BIA provides a calculation framework of the annual financial impact on the health system when implementing a new intervention. Recommendations on how to analyse the financial impact are often included in a subsection of the guideline, because a BIA brings along specific technical requirements.

5.3 Emerging changes

To perform multi-country economic evaluations in an efficient way, close collaboration between HTA agencies and the EMA is essential. At the time of writing, EUnetHTA, as a facilitator of a joint HTA process on a European level, together with EMA is developing a new regulation on HTA. The new

regulation is focused on both joint clinical assessments as well as joint scientific consultations and aims to establish 'a support framework and procedures for the cooperation of Member States', and 'common rules and methodologies for the joint clinical assessment of health technologies' [72]. The new regulation should be applied as of 2025, and is intended to become a permanent framework for international cooperation on HTA [73]. Thus far, the joint work seems to be focused on clinical assessment rather than health economic assessment. Nonetheless, regarding the economic evaluation as a part of the COVend project, it is important to follow the development of the methodological and procedural guidance on joint HTA and to align with it, in order to design and perform an HEE that meets commonly accepted rules and methodologies as much as possible.

5.4 Summary

Considering the variation in contextual factors of the countries, differences in key recommendations on HEE may be unsurprising. The main differences in key recommendations were found in the perspective of the analysis and the choice of comparators. Of less importance, although substantial, is the difference in discount rates, which can be easily adjusted in the model. Nonetheless, similarities in HEE guidance outnumber the differences. The shared preference for the EQ-5D tool to measure utility is highly relevant to the IXION trial. The tool has been included in the clinical study protocol. The new EU-regulation on joint HTA may provide relevant opportunities to reconcile differences among HEE guidance.

6. Recommendations for health economic evaluation in COVend

Prior to the development of an economic evaluation of the costs and consequences of FX06 in the treatment of hospitalised COVID-19 patients, it is essential to gain insight into the use and role of HEE in the reimbursement process. Overall, the necessity of HEE is increasingly being understood among countries, as described in Chapter 4. This underlines the need for and relevance of evaluating FX06 from a health economic perspective.

More specifically, successful implementation of reimbursable inpatient medicines in Europe stands or falls with the inclusion into a hospital formulary. Safety and effectiveness are key elements in the decision on whether to include the pharmaceutical in the HPF. Moreover, a hospital's PTC assesses the financial impact of the therapy on the hospital budget, as well as the expected position of the new therapy in the existing treatment regimen. In the context of FX06, a BIA will inform decision-makers on the costs of FX06 and could identify whether FX06 can substitute, expand, or can be combined with currently used treatment options. We would like to address the relevance of a dynamic BIA, which can be adjusted to the context of public hospitals across Europe.

Though HEE guidelines within Europe are relatively comparable, the result of the exploratory analysis of HEE guidelines (Chapter 5) indicates that the health economic model needs to be designed in a dynamic way, in which the model structure and its input parameters can be easily adjusted by both modellers and assessors. However, as the perspective is a fundamental component of an economic model, and the primarily recommended perspective differs across countries, it may be considered to develop two or more model variants, based on the perspective used. A perspective-based model is supported by the fact that the identification, valuation, and measurement of indirect costs of each country is a resource-intensive and time-consuming task, while even its inclusion in the HEE is not required in most countries. Alternatively, the generalisation of input values related to a societal perspective across Europe can be investigated. However, because of the different context in each country, indirect costs related to productivity loss may be difficult to generalise.

Based on the content of the present report, we plan to design a CUA, complemented by a hospital-specific BIA. The CUA should ideally include all patient-specific characteristics that are analysed as part of the COVend project (WP 4). These characteristics comprise molecular profiles, identified by Omics technologies (proteomics, metabolomics and lipidomics), and novel biomarkers, which could influence prognosis and treatment response of COVID-19 patients. The modelling approach for the HEE of FX06 must be determined, and a justified choice goes beyond the scope of the report. The modelling approach is among others dependent on the number and the type of comparators, and the extent to which patient-level characteristics are applicable to FX06 therapy. The identification of relevant alternative treatments for hospitalised COVID-19 patients will be performed as part of D7.3.

The subsequent step in WP7 is to analyse the barriers and facilitators that could affect implementation of FX06 (D7.2). Regarding D7.3, we will need to specify per country to which alternative treatments the FX06 therapy can be compared. The scope of comparators to include differs across countries, as described in Chapter 5. Finally, since QALY-based CUAs are commonly preferred across Europe, and EQ-5D is the primary recommended tool to measure utility, participants of the current WP should stress the relevance of EQ-5D scoring to the clinical partners of COVend. Any missing values due to an unperformed EQ-5D questionnaire would impact the quality and power of the health economic analysis.

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