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Access to medicines in Europe

Delays and challenges for timely patient access

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List of abbreviations

ABPI	Association of the British Pharmaceutical Industry
AEC	Authorization under exceptional circumstances
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spain)
AIFA	Agenzia Italiana del Farmaco (Italy)
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (France)
ART	Antiretroviral Therapy
ATU	Authorization for Temporary Use
BASG	Federal Office for Safety in Health Care (Austria)
BeNeLuxA	Belgium, the Netherlands, Luxembourg and Austria Initiative on Pharmaceutical Policy
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
CDC	Centers for Disease Control and Prevention
CDF	Cancer Drugs Fund (UK)
CED	Coverage with evidence development
CEE	Central and Eastern Europe
CF	Cystic fibrosis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIRS	Centre for Innovation in Regulatory Science
CMA	Conditional Marketing Authorization
CPG	Clinical practice guidelines
CRD	Centre for Reviews and Dissemination
CUP	Compassionate Use Program
DG IPOL	Directorate-General for Internal Policies
DKMA	Danish Medicines Agency
DRUP	Drug Rediscovery Protocol (the Netherlands)
DTC	Drug and Therapeutics Committee
EAMS	Early Access to Medicines Scheme (UK)
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECDRP	European Commission Decision Reliance Procedure
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency

EOF	National Organization for Medicines (Greece)
EOPYY	National Organization for the Provision of Health Services (Greece)
ERP	External Reference Pricing
EP	European Parliament
EU	European Union
EU27	27 European Union countries
EUnetHTA	Joint Action European network for Health Technology Assessment
EUPATI	European Patients' Academy
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FDA	Food and Drug Administration (United States of America)
FDA	Food and Drug Administration (United States)
FIMEA	Finnish Medicines Agency
FINOSE	Finland, Norway, and Sweden HTA collaboration network
G-BA	Federal Joint Committee (Germany)
GDP	Gross Domestic Product
HALMED	Agency for Medicinal Products and Medical Devices of Croatia
HAS	Haute Autorité de Santé (France)
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
HPRA	Health Products Regulatory Authority of Ireland
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
INFARMED	Instituto Nacional da Farmacia e do Medicamento (Portugal)
JAZMP	Public Agency for Medicinal Products and Medical Devices (Slovenia)
JPMDA	Japanese Pharmaceuticals and Medical Devices Agency (Japan)
KFF	Kaiser Family Foundation
LSE	London School of Economics and Political Science
MA	Marketing Authorization
MEA	Managed Entry Agreements
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MSC	Ministerio de Sanidad, Consumo y Bienestar Social (Spain)
MYMI	Multi-Year Multi Indication
NAMMD	National Agency for Medicines and Medical Devices (Romania)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (England)
NIHDI	The National Institute for Health and Disability Insurance (Belgium)

OECD	Organisation for the Economic Cooperation and Development
OGYÉI	Intézet National Institute of Pharmacy and Nutrition (Hungary)
PASLU	Patient Access Scheme Liaison Unit (England)
PBS	Pharmaceutical Benefits Scheme
PEI	Paul Ehrlich Institute (Germany)
PFS	Progression-Free Survival
PhRMA	Pharmaceutical Research and Manufacturers of America
PIM	Promising Innovative Medicine
PPRS	Pharmaceutical Pricing Regulation Scheme (UK)
PrEP	Pre-Exposure Prophylaxis
PRO	Patient-Reported Outcomes
PVA	Price-Volume Agreement
QALY	Quality Adjusted Life Year
R&D	Research and Development
RWE	Real World Evidence
SAM	State Agency of Medicines (Estonia)
SDG	(United Nations) Sustainable Development Goal
SEED	Shaping European Early Dialogues for Health Technologies
SMC	Scottish Medicines Consortium
SUKL	State Institute for Drug Control (Czech Republic)
TGA	Therapeutic Goods Administration (Australia)
TLR	Time-Limited Resolutions
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)
UK	United Kingdom
VBP	Value-Based Pricing
VPAS	Voluntary Scheme for Branded Medicines Pricing and Access (UK)
W.A.I.T.	Waiting to Access Innovative Therapies
WHO	World Health Organisation

Executive summary

Background

Various definitions of access to medicines exist; key aspects of access include, among others, affordability, availability and timely access.

The World Health Organization defines access to medicines using two main metrics: (i) availability, referring to the extent to which new medicines are available in the market for which they are intended, and (ii) affordability, referring to the extent to which prices of medicines are in line with the purchasing ability of healthcare systems and/or patients. Other definitions place more emphasis on the time to market access, rather than affordability, or on the patient access in the post-reimbursement phase of medicines, defined as “the phase that starts when the first patient is treated under a formal reimbursement scheme”.

Access to innovative medicines varies greatly across European countries and remains a concern, especially for the therapeutic areas of oncology and HIV/AIDS.

Significant variations in access exist between European countries due to diverse regulatory settings, differing inclusion criteria for funding decisions, countries’ purchasing power based on gross domestic product (GDP) per capita, healthcare expenditure, and pharmaceutical prices and utilization rates, among other factors.

Objective

The aims of this study are (i) to identify key factors that delay access across Europe, looking at the different stages of a medicine’s lifecycle and focusing on oncology and HIV/AIDS, and (ii) to provide recommendations on key areas of focus that could ensure affordability and enable faster patient access and availability.

Methods

An analytical framework identified the main policies/activities which can influence patient access across three main pillars of the access pathway:

- a) horizon scanning, marketing authorization (MA), pricing policies, and Health Technology Assessment (HTA) informing pricing/reimbursement decisions.
- b) decision-making on reimbursement and funding of treatments.
- c) diffusion of treatments after they become available.

Macro-factors, such as economic and cultural factors, were also considered. Secondary evidence was identified through scoping reviews for each stage or theme, looking at what factors may

Geographic scope

The geographical scope of the research covers the 27 EU countries (EU27), Serbia and the UK.

cause delays to patient access in Europe across the market access pathway and, where possible, for specific findings for oncology and HIV/AIDS.

Results

300 sources were downloaded and screened, of which 194 sources were included. Key access challenges identified across the different market access pathway steps include:

Marketing authorization

- Lengthy MA approval times because of clock-stops and/or long timeframes for opinions and decisions to be reached.

Pricing

- Command and control pricing systems, such as External Reference Pricing (ERP), or pricing systems with high administrative or evidence requirements.
- The potential for pricing systems (e.g. ERP) to encourage sequenced product launches.

Health Technology Assessment

- The timing of HTA processes, the length of the HTA process itself, and the time it takes for a positive HTA recommendation to be translated into a funding decision and for a funding decision to be implemented.
- HTA conducted at multiple levels (e.g., national, regional and/or hospital level) may result in differential or fragmented coverage and access.
- Involvement of multiple national HTA and reimbursement authorities in negotiations increases the workload with potential impact on timelines and access.
- Cross-country variation in HTA systems and negotiation processes results in diverging access outcomes for the same medicine in different countries.

Reimbursement & funding mechanisms

- While Managed Entry Agreements (MEAs) are generally considered positive for patient access, their expiry might prove challenging in terms of continuing patient access.
- Rigidities in reimbursement mechanisms and a lack of capacity and/or established legal or regulatory frameworks may impede adaptation to new data and uptake of innovative funding models that would otherwise have the potential to facilitate access to treatments.

Market uptake & diffusion

- Geographical factors (location of patients and care provision), as rural locations may experience slower adoption of new drugs when compared to urban environments.
- Health system and macro-level factors (e.g., the way the system operates, income level and market size). For specific therapeutic areas willingness to pay, and societal priorities may also contribute to patient access.
- Physician adherence to clinical guidance and, specifically, the introduction of new therapies.

- Social stigma around specific disease or against certain groups in society may impact how those diagnosed with certain conditions access treatments.

Considerations for policy change

This study highlights continued access issues across all stages of the market access pathway, and across countries despite the introduction of many schemes and initiatives introduced to optimize the pathway. The evidence points towards the key role of country, region, or policy specific contexts in determining whether a potential negative impact on access results from key stages in the access pathway.

Considerations for policy change and the improvement of major issues in patient access were drawn for each stage of the market access pathway, aiming to provide guidance on short-, medium- and long-term options to overcome challenges to access in Europe and in the context of the upcoming Pharmaceutical Strategy. These recommendations will not apply fully across all countries in Europe. Equally, any intervention may not operate individually or as a standalone solution as the various aspects of the access pathway are closely interlinked and often influenced by each other. Therefore, the following recommendations are presented here as a broader set of salient observations and respective suggestions towards improved access that arise from our analysis.

Marketing authorization

- Focus on horizon scanning and early dialogue to maximize the ability and impact of authorization pathways designed for early patient access.
- Strengthen cooperation between regulatory agencies and national HTA agencies through the establishment of parallel review processes.

Pricing

- Improve the design and implementation of pricing systems and move towards pricing policies that are less administratively complex and consider the therapeutic value new medicines.
- Where necessary, modify certain elements of ERP systems to avoid spillover effects.
- Pricing policies promoting evidence-based price-setting should be implemented in the context of highly specialized therapies.
- Review whether pricing and reimbursement systems allow the greatest value to be derived from novel treatments.

Health technology assessment

- Monitor the time taken for the completion of HTAs and funding decisions.

- Improve coordination of HTA processes in countries with decentralized systems.
- Create special assessment pathways or tailor-made criteria for the evaluation of highly specialized treatments usually associated with high degree of uncertainty due to limited evidence.
- Invest in the infrastructure and development of joint mechanisms for RWE generation and EU-wide registries to address evidentiary gaps and/or in instances where significant uncertainty occurs during the assessment and appraisal process.
- Leverage current cooperation across European countries for health technology assessments.

Reimbursement & funding mechanisms

- Use MEAs or novel funding mechanisms to secure funding in cases of negative reimbursement decisions, particularly in areas of significant unmet need.
- Rely on RWE during reimbursement negotiations, especially considering incomplete evidence across EU countries, to ensure evidence required under MEAs is provided in a timely manner.
- Establish therapeutic area-specific solutions for data generation, budgeting, or other bottlenecks.

Market uptake & diffusion

- Ensure clinical guidelines and or care pathways are as up to date as possible.
- Collect evidence on country-specific factors impeding diffusion of medicines.

Macro-level factors & wider system needs

- Minimize intra-country variations, which may result in inequitable access and population-level disparities.
- Ensure accurate and timely diagnosis and treatment initiation through accessible screening and diagnosis programs and services for key disease areas.
- For HIV in particular, it is important to have measures in place at national/community level to reduce criminalization of HIV and/or related activities and social stigma.
- Conduct and sponsor more research into determinants and hurdles for access to support the refinement of existing tools and the use of novel solutions where possible.
- Strike the right balance between health policy and industrial policy.
- Political will is essential to ensure regulatory pathways and value assessment encourage new medicines to come to market.
- Healthcare systems are constantly and dynamically evolving and need to be able to continuously adapt to changing circumstances.

Conclusion

Patient access remains a challenge for many countries, centered around availability, affordability, time impact, and geographical variation challenges. Time delays occur given the complexity of the access pathway and the multiplicity of stakeholders involved. Unequal access across countries can also result due to the effects of different policies, different health system designs, socioeconomic and cultural factors. Strategic efforts to overcome tensions in the market access pathway include the availability of schemes such as early dialogue, early scientific advice and parallel review, harmonization of evidentiary requirements and common ways to deal with uncertainty and the use of novel funding mechanisms where possible, to ameliorate the availability and affordability of medicines. An improved evidence base for specific aspects of the pathway and for disease areas (such as HIV/AIDS) is needed to allow for monitoring of current systems, informed policy-making, and support both amendments to existing tools and the use of novel and groundbreaking solutions.

In order to reduce the challenges and tensions in the pathway and improve the affordability and availability of medicines across and within countries, decision-makers, governments and purchasers of medicines should ensure that regulatory, pricing and reimbursement processes can adapt to the fast-paced and highly innovative health environment and ensure better health outcomes for patients across countries.

Introduction

Medicines should be accessible, both available and affordable, to health care systems and patients in a timely manner to ensure improved outcomes and contribute to population health. According to the World Health Organisation (WHO), lack of access to medicines is one of the most complex and vexing problems that stands in the way of achieving better health (WHO 2017). The research and development (R&D) in new and innovative mechanisms providing better clinical outcomes for patients is high on the agendas of many key stakeholders and governments. However, regulatory requirements, value assessment processes, and regulated pricing and reimbursement policies implemented across Europe, among other areas, can delay patient timely access to medicines.

Various definitions of access have been developed, serving different purposes and focusing on distinct aspects of access depending on the context, perspective and goals of the healthcare system. Key aspects of access include, among others, affordability, availability, the speed with which accessibility is established, the prioritisation of highly effective medicines and treatments targeting unmet need, and well-functioning healthcare systems which are easily adaptable and well-prepared for the introduction of new and innovative treatments. The WHO defines access to medicines using two main metrics: (i) availability, referring to the extent to which new medicines are available in the market for which they are intended, and (ii) affordability, referring to the extent to which prices of medicines are in line with the purchasing ability of healthcare systems and/or patients (WHO 2010). In the United Nations Sustainable Development Goals (SDGs) more emphasis is placed on the affordability and availability of essential medicines in low- and middle-income countries (WHO, 2020). The European Federation of Pharmaceutical Industries and Associations (EFPIA) uses alternative metrics for access, focusing on time to market access to measure availability, rather than focusing on affordability; EFPIA's Waiting to Access Innovative Therapies (W.A.I.T.) indicator defines access as (i) the rate of availability, measured by the number of medicines available to patients and usually marked by the point when medicines gain access to the reimbursement list, and; (ii) the average time between marketing authorization (MA) and patient access, measured by the number of days elapsing between the date of MA to the date of completion of post-MA administrative processes (IQVIA 2019a). Another approach, distinguishing between market access and patient access, created a patient access indicator to showcase how countries performing well on time to market access do not necessarily perform well on patient access; the patient access indicator targets the post-reimbursement phase of medicines, defined as "the phase that starts when the first patient is treated under a formal reimbursement scheme" (Vintura 2020a).

While existing literature and evidence tends to focus on market, rather than patient access, it is important to recognize market access does not necessarily equate to patient access. Access

should not only be considered in terms of the availability of medicines but also based on the ability of patients to gain access to those medicines, which includes obtaining a prescription for the medicine, the overall affordability for health systems, and the ability to get the right treatment at the right time.

Despite many targeted efforts to ensure availability of medicines and expedite patient access, such as the European Union (EU) Transparency Directive (EC 1998) which sets an 180 day time limit by which medicines should become available on the European market after pricing and reimbursement decisions, evidence from the literature suggests that access to innovative pharmaceuticals in Europe is still challenging across different therapeutic areas and indications (Angelis, Lange, and Kanavos 2018). Across EU member states, significant variations in access exist between Western and Eastern European countries due to diverse regulatory settings, differing inclusion criteria for funding decisions, countries' purchasing power based on gross domestic product (GDP) per capita, healthcare expenditure, and pharmaceutical prices and utilisation rates (Vogler et al. 2017). Oncology data from the 2020 EFPIA Patients W.A.I.T Indicator survey shows that availability of recently approved medicines varies: only 10% of recently approved medicines are available to patients in Latvia in comparison to Germany, where patients have access to all newly European Medicines Agency (EMA) approved medicines (IQVIA 2021), at least one year post-EMA MA. Differences in how long patients have to wait for products to become available also exist: the time-to-availability indicator, which measures the days between MA and the date of availability to patients within countries, shows patients in Serbia and Bulgaria may wait up to almost 31 and 23 months, respectively, for newly authorized medicines for oncology to become available compared to German patients who gain access within four months (IQVIA 2021).

Differences in healthcare policies and the administrative complexity of pricing and reimbursement regulations and health technology assessment (HTA) systems may create tensions which can, subsequently, result in variation in medicines' availability and affordability across European countries. Even when medicines receive a positive HTA recommendation, access is still not a guarantee and may be determined by further contextual factors. Negotiations and agreements between purchasers/commissioners of care and manufacturers have been shown to pose further delays, while discrepancies across European countries may result in unequal access: there are limited access delays after EMA approval in the United Kingdom (UK)¹, where the NHS should fund the treatment within three months after HTA recommendation and Germany, where the additional benefit of the pharmaceutical over its comparator should be established within three months after MA, while other countries experience substantial delays

¹ The United Kingdom exited the European Union on the 31st of January 2020. The examples and data used in this report are most commonly from before this date but are signposted if they occurred after the exit or supplemented by additional information on the current situation where useful.

due to formal reimbursement procedures like France, Belgium, and Italy (Ades et al. 2014). In addition, the involvement of multiple stakeholders (such as purchasers/commissioners of care, regulators, national and regional competent authorities for pricing and reimbursement, the healthcare system itself, the pharmaceutical industry, patients or patient associations and carers) in the formal process of value assessment and coverage negotiations may facilitate availability and affordability, but can also create access challenges in terms of the promptness with which these technologies become available.

There is a need to identify where challenges are created across the lifecycle of a medicine and to understand the areas of the market access process efforts of policy- and decision-makers should target. This study attempts, via secondary evidence, to (a) contribute to the review, analysis, and body of information about challenges created during marketing authorization, pricing policies and other factors which can impede uptake and diffusion of new treatments and (b) discuss different reimbursement and funding pathways that could be pursued to ensure optimum access. The objectives of this study are twofold: first, to identify key factors that delay or hinder access across Europe, looking at the different stages of a medicine's lifecycle and focusing on oncology and human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS), and second, to provide recommendations on key areas of focus that could ensure affordability and enable faster patient access and availability.

Analytical framework

The analytical framework for this study extends and complements existing frameworks which studied access challenges and patient access delays (Angelis et al. 2018; Kanavos et al. 2017; Vintura 2020b). Five main stages of a medicine's pathway to patient access and relevant potential factors (policies/main activities) were identified from the aforementioned studies and a further literature search of factors associated with market access delays and patient access (Deloitte 2019; Vintura 2020b).

The analytical framework (Table 1) identified the main policies or activities which can potentially influence patient access during the access pathway. The analytical framework, visualized in Figure 1, is divided in three main pillars which relate to the pathway medicines follow before and after they become available in a market and other external factors which are likely to have implications on patient access along the access pathway. Our framework focuses on processes a medicine should follow to secure presence on the market (such as regulatory policies, pricing, evaluation and reimbursement, uptake of clinical guidance, and prescribing adherence) and avoid using the word 'barriers' to reflect that these processes are key enabling components of the access pathway. Instead, 'tensions' and 'challenges' are used interchangeably to refer to the potential impact arising from the interaction between or the nature of specific processes throughout this pathway on patient access.

The *first pillar* of the analytical framework includes key steps, policies and tools that are implemented prior to and contribute to decision-making on reimbursement and funding of medicines in order to become available at national and regional level: (i) horizon scanning, (ii) marketing authorization (MA), (iii) pricing policies, and (iv) HTA informing pricing/reimbursement decisions. Evidence is presented at an aggregate level, examining whether these policies can potentially cause delays in market access and impede patient access. Both direct endpoints reflecting timelines and time delays and indirect endpoints such as policy procedures and implementation and evidentiary requirements were selected to show how challenges for patient access can be either created or overcome in the presence of these policies. Other endpoints, which might have an impact on patient access, identified in the literature were also selected for review (Table 1).

The *second pillar* focuses on the process of decision-making on reimbursement and funding of treatments while taking into consideration tools and outcomes from the stages of the first pillar such as pricing and HTA. This pillar ensures patient access or enables availability and/or faster access at national or regional level, to medicines which might be highly innovative, very costly to purchasers/commissioners of services or accompanied by less comprehensive clinical data than normally required.

The *third pillar* of the framework focuses on the diffusion of treatments after they become available at national and regional level including endpoints on patients' uptake and healthcare system organisation. Beyond these three pillars, the analytical framework includes a summary of macroeconomic factors, the burden of disease and country-specific political issues that can influence patient access horizontally and throughout all the stages of medicines access pathway with a focus on oncology and HIV/AIDS to give an overview of the economic, political, and epidemiological context of each market and to investigate if these factors might have any relation to patient access delays.

The analytical framework developed for the literature search is presented in Table 1. The study is structured across five stages outlined in the framework including: (i) marketing authorization, (ii) pricing policy, (iii) HTA informing pricing/reimbursement decisions (iv) reimbursement pathways and schemes and (v) market uptake and diffusion.

Figure 1: Components of market access pathway and patient access

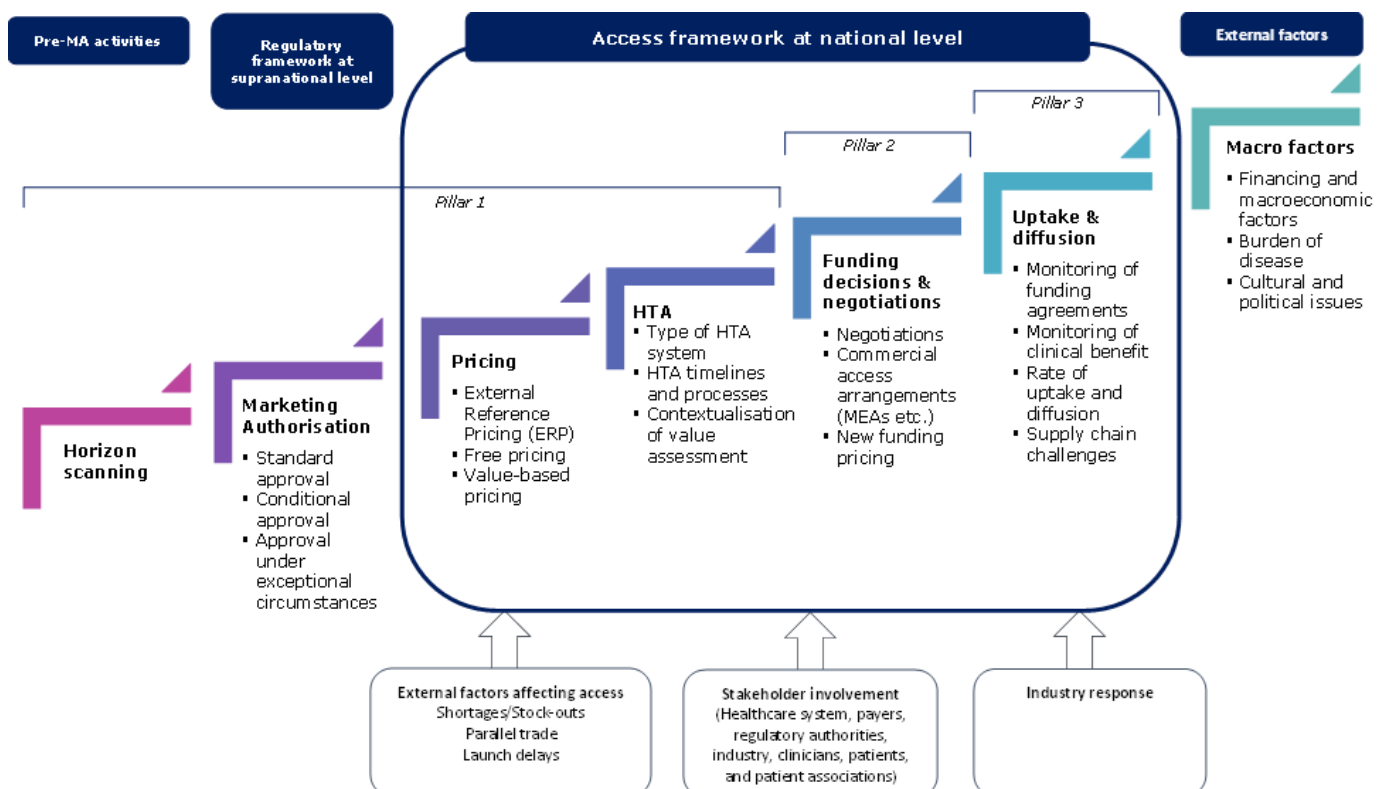


Table 1: Analytical Framework

Pillars	Stage	Policies/main activities	Endpoints
1. Patient access prior to funding decision-making	Marketing authorization	<ul style="list-style-type: none"> Standard MA Accelerated MA Conditional MA Parallel Review Authorization under Exceptional Circumstances 	Timelines and time delays Policy procedures and implementation Evidentiary requirements Additional schemes facilitating market and patient access at regulatory level
	Pricing	<ul style="list-style-type: none"> External Reference Pricing (ERP) Free Pricing Value Based Pricing (VBP) Rate of Return Regulation Other administrative interventions affecting pricing (e.g., price cuts) 	Timelines and time delays Policy procedures and implementation Evidentiary requirements Company and distributor strategy Policy outcomes
	Health Technology Assessment	<ul style="list-style-type: none"> Independent HTA Integrated HTA 	Timelines and time delays HTA assessment Policy procedures and implementation Other initiatives facilitating market and patient access at HTA level
2. Reimbursement & funding decision-making	Pricing and reimbursement negotiations	N/A	Timelines and time delays Policy procedures and implementation Evidentiary requirements
	Commercial access agreements	<ul style="list-style-type: none"> Managed Entry Agreements (MEAs) 	Timelines and time delays Policy procedures and implementation Evidentiary requirements
	Institutional funding mechanisms	N/A	Type of arrangements and circumstances Reviews aimed at adapting and updating funding mechanisms Policy procedures and implementation
	New funding mechanisms	<ul style="list-style-type: none"> Contracting/Over-Time Models Portfolio Agreements Re-Insurance Models 	Outcomes Timelines and time delays Policy procedures and implementation Evidentiary requirements
3. Diffusion and uptake	Market uptake and diffusion	N/A	Impact of purchasing and procurement agreements Supply chain challenges Patient uptake
Other factors influencing patient access	Macro-factors	<ul style="list-style-type: none"> Economic factors Patients' socioeconomic status Healthcare system characteristics Burden of disease and epidemiology Cultural and political issues 	Patient access

Source: The Authors.

Methods

Secondary evidence was collected through a set of scoping reviews focusing on factors influencing market access throughout the lifecycle of medicinal products (MA, pricing, HTA, reimbursement and funding negotiations and product diffusion into the market) across Europe.

Therapeutic scope

The study focuses on the therapeutic areas of HIV/AIDS and oncology. Oncology was included in this study considering the accelerated pace of new therapies coming to market in recent years, the significant challenges associated with clinical benefit assessment, cost-effectiveness and funding decisions, all of which can influence patient access (Martinalbo et al. 2016). Similarly, impressive achievements have been seen in the therapeutic area of HIV/AIDS ever since the Centers for Disease Control and Prevention (CDC) first reported cases of HIV/AIDS in 1981 (CDC 1981a, 1981b). Despite this, however, HIV/AIDS continues to be a major global public health issue. Significant gaps in HIV/AIDS care remain due to structural components such as legislation, as well as issues of stigma, discrimination and lack of general acceptance in society (Zaidi 2013). Based on available evidence, treatments for both oncology and HIV/AIDS are associated with high costs (Martinalbo et al. 2016; Reich and Bery 2005; Zaidi 2013), launch sequencing (Reich and Bery 2005; Uyl-de Groot et al. 2020) and are often prioritized by health care systems in Europe (Aggarwal, Ginsburg, and Fojo 2014; Zaidi 2013). Finally, the presence of strong patient organizations in both disease areas are known to influence patient and market access (Aggarwal et al. 2014).

Geographical scope

The geographical scope of the research covers the 27 European Union member states (EU27), Serbia and the UK. The countries were selected to capture the characteristics of the various markets in Europe. Beyond the EU27, two additional countries were included: the UK, as it recently exited the EU, and Serbia, as an EU accession country².

Literature review

Due to the extensive scope of this study, which considers all stages of a treatment's lifecycle when entering a market, conducting a systematic literature review was not possible due to difficulties in a) capturing all the possible resulting tensions and challenges for patient access in light of the extensive available evidence and b) complying to the rules of systematic literature reviews (CRD 2009). Instead, scoping reviews for each stage of a treatment's lifecycle were

² A country which is a candidate for membership of the European Union.

conducted. Scoping review search strategies were designed in a way to enable the generation of the maximum relevant evidence against the study research question. A detailed description of the scoping review is outlined in Appendix 2.

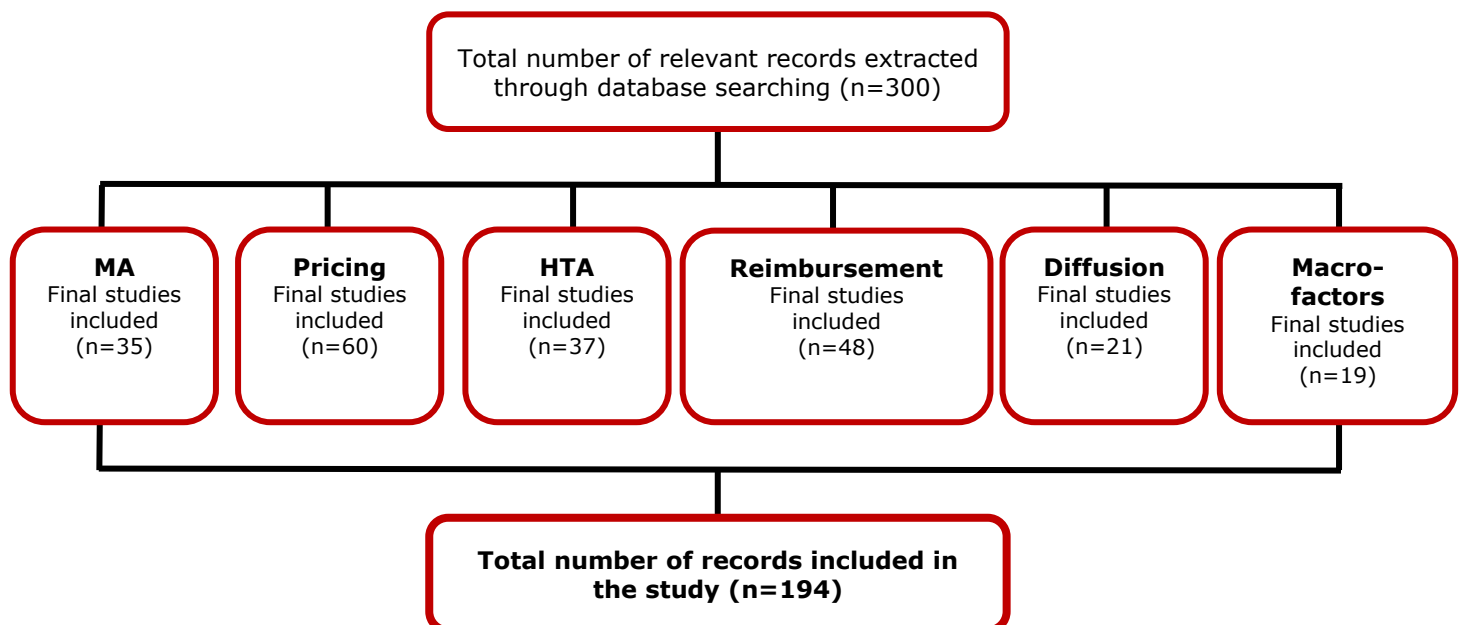
Limitations

This study is not without limitations. First, while the conceptual framework aimed to capture all the different stages of the market access pathway to identify tensions and challenges for access, it remains difficult to isolate the impact each stage has on patient access, availability and affordability. Similar difficulties potentially exist if treatments follow a deterministic pathway, where an initial action, step or stage determines or has implications for a later outcome or stages. The dynamic nature of all these processes, and the resulting difficulties in identifying precisely at what stage key tension is created limits the generalizability and robustness of the body of literature identified in this study. Second, careful interpretation of the identified evidence is required. As this study covers a very broad geographical scope comprising different healthcare systems and other macro-economic factors specific across settings, substantial variation in access has been observed, limiting our ability to establish common trends across settings. Third, the literature was scanned using online databases with results limited to English. Therefore, it may be that evidence from some EU countries was not captured due to the language limitation. Fourth, no risk of bias assessment was performed on the studies and sources included, therefore this study draws no conclusions on any potential biases in results or conclusions of the included studies. Finally, results from this study may be inconclusive as evidence on the impact of the policies covered by the framework on access to medicines utilized in this study are predominantly descriptive in nature due to a lack of quantitative studies and relies on non-peer reviewed literature in some cases.

Literature review results

Given the magnitude of potentially relevant literature on market access, we limited the number of included records to a maximum of 60 relevant studies for each theme. The selection was made based on the established relevance to the search terms (dictated by the order of the results, frequency of search terms in titles, and relevance to the endpoints), or results with a form of meta-analysis or with a focus on compiling recent evidence on the topics (for example, existing systematic literature reviews). The full texts of 300 relevant studies were downloaded. As the scoping review was conducted simultaneously by different members of the research team, studies with relevant information for more than one stage were considered. In total, 194 studies were included in this review. The results of the scoping review for each stage of a treatment’s pathway are presented in Figure 2. The following sections (Sections 5 to 13) summarize the available evidence.

Figure 2: Flow diagram with search results from the scoping review



Marketing authorization

Pharmaceutical manufacturers should apply for a marketing authorization to the competent regulatory authority to gain market access in Europe. According to the type of medicine undergoing evaluation and the evidence submitted by the applicant, there are different types of marketing authorization pathways and schemes a medicine can go through in order to achieve MA. This section covers the impact of the available regulatory pathways and schemes and patient access looking into time delays, policy procedures and implementation, evidentiary requirements, and the presence of additional schemes facilitating market and patient access at regulatory level.

Timelines and time delays

Marketing authorization pathways. In EU member states, manufacturers can apply for MA of new products through four different pathways: (i) centralized, (ii) national, (iii) mutual recognition and (iv) decentralized, although the centralized procedure is mandatory for marketing authorization applications of new active substances within the therapeutic areas of oncology and HIV/AIDS. Applications for multiple Member States for products that do not fall within the mandatory scope of the centralized procedure must follow the mutual recognition procedure or the decentralized procedure.

The official timelines for the assessment of a MA application for a new medicine is set to 210 active days³ for the centralized, decentralized, and national procedures, and 120 active days⁴ for the mutual recognition procedure. In Serbia, the EU timeframe of 210 days is applied for national MA procedures (Medicines and Medical Devices Agency of Serbia n.d.). In new guidelines on MA routes post-Brexit (MHRA 2021), the Medicines and Healthcare products Regulatory Agency (MHRA) has introduced (i) a rolling review for MA which takes 160 days and (ii) a European Commission Decision Reliance Procedure (ECDRP) which takes approximately 67 days (if the application is submitted within five days of the opinion of the EMA Committee for Medicinal Products for Human Use (CHMP)). Post-Brexit decentralized and mutual recognition procedures will still be available in the UK.

Time to marketing authorization. The overall median approval time taken by the EMA for all the approved new active substances was about 423 days⁵ in 2019 compared to the official timelines of 210 days, with an average of 270 days for accelerated assessments, 481 days for conditional approvals and 281 days for high priority medicines (Rodier et al. 2019).

³ For the decentralized procedure, the 210 days is made up of: 120 days for the assessment by one of the member states plus 90 days for other member states to recognise the marketing authorization.

⁴ 90 days for the recognition of the decision of the reference member state plus 30 days for the national authorization.

⁵ Including clock-stops.

Several studies found the EMA application process takes longer than the US Food and Drug Administration (FDA) MA application process (CIRS 2020; Hartmann, Mayer-Nicolai, and Pfaff 2013; OECD 2020; Rodier et al. 2019; Shah, Roberts, and Shah 2013). The Centre for Innovation in Regulatory Science (CIRS) reported median approval times for oncology drugs and immunomodulators between 2015 to 2019 were the longest for Swissmedic (450 days) followed by the EMA (419 days), the Australian Therapeutic Goods Administration (TGA) (352 days), Health Canada (345 days), the Japanese Pharmaceuticals and Medical Devices Agency (JPMDA) (284 days) and the FDA (239 days) (CIRS, 2020).

A recent study on access to oncology medicines found the MA process in the European Economic Area took 13 months compared to only 7 months for the US FDA (OECD, 2020). Additionally, a study on oncology products approved between 2005 and 2013 found MA submissions to the FDA were made on average 28.4 months earlier than submissions to the EMA (Samuel and Verma 2016). The availability of products also differs between the FDA and the EMA: the FDA approved 170 new drugs while the EMA approved only 144 between 2011 and 2015, with the FDA approving more orphan drugs than the EMA⁶ (Downing, Zhang, and Ross 2017).

Time from marketing authorization to patient access. The average time between MA and patient access, defined as the time taken for a medicine to reach patients after MA, calculated by the average number of days taken to complete all post-MA processes, increased between 2007-2009 (with an average duration 233 days) and 2014-2016 (with an average duration of 318 days) in 13 out of 14 European countries, with the exception of Switzerland; the largest increase in the number of days between MA and post-MA activities was seen in Portugal (an increase of 288 days from 2007-2009 to 2014-2016), Ireland (251 days from 2007-2009 to 2014-2016), and Austria (241 days from 2007-2009 to 2014-2016) (Deloitte 2019).

Accelerated approval pathways. Besides the standard pathways of MA, conditional marketing authorization (CMA), authorization under exceptional circumstances (AEC), and accelerated MA have been introduced in Europe to facilitate access to medicines. The CMA procedure is designed as a fast-track approval of medical products, giving patients faster access to new therapies and simultaneously ensuring the required time for manufacturers to collect the additional evidence required to subsequently obtain a standard MA. Mixed evidence is reported on the effect of CMA on market access: the EMA's experience between 2006 and 2016 demonstrated CMA was successful as an important tool for ensuring timely access to medicines (EMA 2017b). According to a report on the 10-year experience of CMA use by the EMA, products accepted under CMA obtained MA four years earlier, on average, when compared to MA obtained through a standard procedure (EMA 2017b). On the other hand, a recent study on EMA-authorized oncology drugs (Garsen, Steenhof, and Zwiers 2021) found CMA to increase the total procedure time by 24 days

⁶ 43.5% of the approved agents in the US were orphan drugs, while in Europe only 25% were orphan drugs

for small molecules, though time decreases for the total procedure were still observed for biotechnology-derived products, with a decrease of 35 days in duration (Garsen et al. 2021). Taking the aforementioned results into consideration, the study concluded CMA only has a mild effect on procedure times (Garsen et al. 2021). The impact of CMA on facilitating patient access may be further debatable, as delays may occur in later stages of the market access pathway: for example, variable outcomes from HTA appraisals may occur due to uncertainties arising from the economic and/or clinical evidence of these medicinal products authorized under CMA or other early access mechanisms (Spearpoint, Yip, and Zhang 2014; Tzouma et al. 2017).

Authorization under exceptional circumstances. Before the introduction of CMA in Europe, one in four oncology products were authorized under exceptional circumstances (Martinalbo et al. 2016). However, AEC has been used less following the introduction of CMA in the European system (Martinalbo et al. 2016). This form of authorization is given for medicinal products where the collection of comprehensive data on safety and efficacy is faced with challenges, because of reasons such as the condition to be treated is rare or the collection of full information is not possible or is unethical. AEC can potentially be considered as a positive factor in facilitating patient access as the procedure gives medicinal products which do not meet the evidentiary requirements to be granted a standard MA access to the market.

Accelerated MA. In a recent study on newly EMA-authorized oncology drugs, the effect of accelerated MA on patient access was reported to be significant compared to other types of MA in Europe (Garsen et al. 2021). The study demonstrated that accelerated MA had the greatest positive impact on decreasing MA time (compared to other forms of MA) for both small molecules and biotechnology-derived products, with a reduction in total procedure timelines from 370 to 200-215 days (Garsen et al. 2021).

Policy procedures and implementation

Procedural issues. The literature suggests delays in patient access related to MA in Europe is driven by the need of clock-stops⁷ during the review process which are being implemented when additional evidence or clarifications are required. Studies on differences in length of approval time between the EMA and the American Food and Drug Administration (FDA) found that EMA approval times were significantly longer (Hartmann et al. 2013; OECD 2020; Rodier et al. 2019; Shah et al. 2013) due to clock-stops during the review process and the time taken to receive the EMA's expert advisory opinion and a final decision by the European Commission (EC) after a positive opinion by the CHMP which is usually given within 67 days (Hartmann et al. 2013; OECD 2020). A study on approval of oncology products in between 2006 and 2011 found a median

⁷ A period during which the evaluation of a medicine is officially stopped, while the applicant prepares responses to questions from the regulatory authority. The clock resumes when the applicant has sent its responses.

approval time of 13.3 months (95% confidence interval (CI): 12.5-14.4 months), a median active review time⁸ of 6.6 months (95% CI: 6.5-6.7 months) and a median clock-stop time of 4.2 months (95% CI: 2.9-4.9 months) for oncology products approved by the EMA (Hartmann et al. 2013). Interestingly, the CIRS found company response timelines to be a significant factor influencing approval times as they were demonstrated to be a driver behind the sudden increase in the overall median EMA approval times in 2018 (Rodier et al. 2019).

Sponsor size. The size of the sponsor (pharmaceutical company) may significantly influence the total timeline for approval, driven by longer total clock-stop times and first clock-stop⁹ time for small-sized companies (Garsen et al. 2021). In a recent study on the EMA, MA applications for oncology drugs for the authorization of small molecules from small-sized companies had longer timelines of 483 days, when compared to 356 days for medium-sized and large companies (Garsen et al. 2021).

CMA review timelines. Review timelines are demonstrated to be longer for CMA compared to standard MA, having a modest positive non-significant effect on clinical development times (Boon et al. 2014). The study concluded that this effect is due to a lack of sufficient incentives for companies to request CMA and that CMA is perceived as a 'rescue' option by regulators and companies, rather than a prospectively planned pathway to provide early access. However, it should be noted this study is from 2014 and the EMA have since introduced several other initiatives to facilitate early access alongside CMA, such as early dialogue. The EMA notes that CMA should be combined with early dialogue and prospective planning to facilitate timely access (EMA 2017b). A study from 2010 investigated the differences in approval times between standard authorization and conditional approval of medicinal products for HIV/AIDS and oncology by looking at both review times and clinical development times. The study found conditional approvals to be associated with longer review times, but with simultaneous shorter clinical development periods influencing timely market access positively (Boon et al. 2010).

AEC review timelines. Total review timelines might be longer for drugs qualifying under the AEC in comparison to CMA: CMA can change into a standard authorization once data collection requirements are fulfilled by the manufacturer, while products authorized under exceptional circumstances do not lead to standard MA and the risk-benefit profile is reassessed annually. When investigating differences in approval times of medicinal products for HIV/AIDS and oncology across various MA options, Boon et al.(2010) found that authorization under exceptional circumstances is associated with longer clinical development periods due to challenges in recruiting patients and executing clinical trials, and did not accelerate the approval

⁸ Calculated as intervals between the start of the centralized procedure (i.e. 'day 0'), the date of the initial CHMP opinion or the withdrawal decision, and the date of the EU Commission decision.

⁹ During a clock-stop, the evaluation is paused while the applicant prepares the responses to the CHMP's questions and updates the medicine's risk management plan.

process of innovative medicinal products compared to standard authorization (Boon et al. 2010). The study further found that review process times for exceptional circumstances drugs were longer by approximately a month due to longer clock-stop periods (Boon et al. 2010).

Accelerated MA review timelines. On the other hand, accelerated MA is associated with shorter review times, but the workload can be assumed to be heavier considering the additional preparation and application review in comparison to the standard MA application. According to a review by the EMA on its experience with accelerated assessment, the accelerated assessment scheme was found to result in increased levels of dialogue between the EMA and applicants and has since received positive feedback on the quality and timeliness of interaction with applicants (EMA 2017b). The review highlighted that keeping shorter timelines is challenging and requires “meticulous” planning (EMA 2017b). Review times by the CHMP and EU Commission for accelerated MA processes are shorter when compared to the official timelines of the centralized process (from 210 days to 150 days) (Rodier et al. 2019). A study also found company response times to be four times faster during accelerated MA procedures when compared to standard MA, though company response times were observed to increase from 2014-2016 to 2017-2018, while the time taken by the EU Commission and EMA for review decreased in that same time period (Rodier et al. 2019).

Evidentiary requirements

There are no differences in evidentiary requirements for accelerated MA when compared to standard MA, except for a justification of the eligibility¹⁰ of the product subject to accelerated MA to be provided by the manufacturer in their accelerated MA application. However, considering the significantly shorter review times for accelerated MA when compared to standard MA, the time taken for this additional evidentiary requirement is not expected to be significant when looking at market access.

AEC products are accepted based on less comprehensive data than standard MA in cases where the collection of comprehensive data on efficacy and safety under normal conditions are challenging (e.g. the treated condition is rare or the collection of full information is not possible or is unethical) (EMA n.d.). This type of MA gives patient access to medicines which would have not been otherwise authorized under standard procedures.

Similarly, CMA may facilitate faster patient access by authorizing medicinal products based on less comprehensive clinical data than required for a standard MA while giving manufacturer’s time to collect more comprehensive data. Manufacturers granted a CMA are obligated to fulfil set requirements (Appendix 1), such as collecting new evidence through studies for the EMA to confirm the medicine’s benefit-risk balance (EMA n.d.). The CMA is valid for a year and can be

¹⁰ Medicines should be of major interest for public health and therapeutic innovation to be eligible for accelerated MA.

renewed annually until the manufacturer can present the full data for the product to obtain a standard MA.

Additional schemes facilitating market and patient access at regulatory level

Horizon scanning

Horizon scanning. To ensure timely patient access to new technologies, horizon scanning activities are increasingly performed at the national (e.g., the National Horizon Scanning Centre (NHSC) in the UK) or more recently at the supranational level (e.g., the International Horizon Scanning Initiative (IHSI) in Belgium, the Netherlands, Denmark, Ireland, Luxembourg, Norway, Portugal, Sweden and Switzerland), helping governments and health authorities to identify the potential financial, clinical, or organizational impact of new health technologies prior to their arrival in the market (Ijzerman and Steuten 2011; LSE 2020). The main goals of these activities vary across countries but is often used to enable healthcare systems to better prepare their budgets and resources for the introduction of new technologies in the market. In turn, this can ensure timely and efficient processes throughout all stages of a treatment's market access pathway. For instance in England, horizon scanning helps in product selection for HTA assessment, managed introduction and monitoring of drugs, informing health care providers and managers, is used in budget forecasting and planning services (LSE 2020). Through these activities, notification for new technologies are made to NICE 20 months before MA (Ciani and Jommi 2014). In the Netherlands and Sweden, horizon scanning does not only help with the selection of medicines but also informs price negotiations (Lepage-Nefkens et al. 2017). At the supranational level, horizon scanning can significantly contribute to faster national assessments and market access through shared information about the costs and launch sequencing strategies for new technologies (IHS Markit 2019). At the same time, joint horizon scanning can help to reduce duplication of effort for manufacturers and decision-makers by setting central data collection requirements for new medicines across the member states (IHS Markit 2019). According to the literature horizon scanning can also help manufacturers to anticipate potential tension affecting market access and help them proactively work to overcome these by shaping the market and engaging stakeholders (Ciani and Jommi 2014).

Early dialogue, parallel scientific advice, parallel review and scoping

The use of early dialogue and parallel scientific advice can expedite and facilitate patient access (Balaisyte, Joos, and Hiligsmann 2018; Deloitte 2019; Gannedahl, Udechuku, and Bending 2018; Martinalbo et al. 2016). Currently, early dialogue in the form of early scientific advice is offered in Europe either by regulatory agencies, HTA bodies or through integrated parallel advice provided jointly by regulatory agencies and HTA bodies. On a multi-national level, schemes such as the EU Shaping European Early Dialogues for Health Technologies (SEED) programme and

parallel consultation processes have been introduced as collaborative efforts between the EMA and the Joint Action European network for Health Technology Assessment (EUnetHTA) to foster cooperation between national regulators and HTA bodies and harmonize regulations across EU member states to facilitate access to medicines.

Early dialogue and SEED. In Europe, early dialogue is used to create pipeline awareness and, more importantly, initiate communication between stakeholders. Early dialogue in the form of early scientific advice is considered essential for both the industry and regulatory agencies to ensure a common understanding and to reach agreements regarding scientific and economic requirements for regulatory approval (Balaisyte et al. 2018; Deloitte 2019; Gannedahl et al. 2018; Martinalbo et al. 2016) and has proven to reduce the possibility of rejection by EMA (Gannedahl et al. 2018). A study looking at the challenges related to market access of advanced-therapy medicinal products showed that numerous advanced therapy medicinal products in the United States (US) and Europe successfully managed to obtain market access, though these products failed to secure reimbursement due to insufficient comparative effectiveness data and the shift of countries towards value-based models for reimbursement (Driscoll et al. 2017). The authors discussed that the demonstration of incremental benefit of these treatments against therapeutic alternatives could be achieved through engagement with purchasers, especially prior to the commencement of pivotal trials, and programmes such as the EU SEED programme which can ensure early planning and greater harmonization in requirements across Europe in order to secure reimbursement and further reduce market access delays (Driscoll et al. 2017).

The parallel consultation scheme. The parallel consultation scheme offers feedback to pharmaceutical companies for multi-national product-launches in the EU regarding evidence requirements of both regulators and HTA bodies, to aid addressing issues where perspective and evidence requirements might differ across different member states. In England, joint scientific advice from the MHRA and National Institute for Health and Care Excellence (NICE) was established to provide detailed exploration of HTA and regulatory issues and ensure that manufacturers' development plans produce evidence which can be relevant for future HTA assessments performed by NICE. During this process, manufacturers can seek advice on clinical trial design and analysis and on their economic analysis (National Institute for Health and Care Excellence, 2021). Overall, the parallel consultation process is thought to streamline and make the process potentially less resource-consuming by engaging multiple HTA-bodies at once (Balaisyte et al. 2018). Feedback from the pharmaceutical industry on the parallel consultation process is positive, which highlights the pharmaceutical industry's appreciation of the possibility for early discussions with regulators and HTA bodies (Balaisyte et al. 2018). Possible future developments highlighted in the literature include improved synergies between HTA bodies and the EMA requirements to avoid duplication of work and confusion (Balaisyte et al. 2018).

Parallel review. Parallel review where a treatment can undergo evaluation of marketing authorization and reimbursement in parallel as seen in Australia and Canada¹¹ have not yet been introduced in Europe. Only in England a form of parallel review for oncology medicines was introduced under the establishment of the new Cancer Drugs Fund in 2016, where NICE appraisal process should start earlier in order to have a draft HTA guidance prior to MA. However, the final HTA guidance can be published within 90 days of MA (NHS England 2016).

Scoping. In most European countries the pricing and reimbursement process cannot start until full EMA approval is granted. Therefore, scoping refers to the phase in-between regulatory approval and initiation of the pricing and reimbursement process, whereby an initial “scoping” analysis can be performed for the purpose of determining the full scope of the upcoming HTA appraisal. It is valuable in building knowledge and awareness of a disease entity and define the clinical context of the technology in question by discussing mainly its target population, clinical outcomes, and therapeutic alternatives. This offers the opportunity to inform the appraisal process prior to MA about the quantity and quality of the available evidence and hence, optimize time to reimbursement decision making and patient access. According to an analysis performed by the European network for HTA, only 16 (out of 29 participating member states) engage in scoping discussions for pharmaceuticals prior to the pricing and reimbursement procedure and variation exists on the timing when scoping occurs. For example, the Spanish agencies define the scope only about 1 to 3 weeks just before the assessment starts, while other agencies engage in scoping discussions discussed well in advance before the start of the appraisal, such as 90 days in Belgium, 1 to 4 months in England or up to 6 months in advance in Ireland (EUnetHTA 2018). Early scoping is likely to increase the relevance and feasibility of the HTA procedure for all relevant stakeholders and it is therefore highly recommended as an integral part of each HTA system (Oortwijn et al. 2017).

Compassionate use programmes

At the stage of pre-authorization, new medicinal products can be first made available to patient through clinical trials. Patients may further be able to access pre-authorized medicines through compassionate use programs (CUP) which provide access on a cohort level or on a named patient

¹¹ In Australia, manufacturers can apply for parallel assessment when treatments are a first-in-class medicine, a medicine with a co-dependent technology, a new medicine for a condition that is currently treated or an already listed medicine for an additional condition. Positive HTA recommendations are conditional on MA approval (PBS, 2020). In Canada, an aligned review process was launched in 2018 as a joint initiative of the Canadian regulatory body, the national HTA body, and the HTA body in Quebec. This initiative established an information sharing process was established and manufacturers applying for pre-marketing authorization can do so up to 180 calendar days prior to the anticipated date of market authorization offering the potential to substantially reduce the time interval between MA and HTA recommendations (The Canadian Agency for Drugs and Technologies in Health, 2019).

basis. Compassionate use programs might be offered to patients with life-threatening or seriously debilitating conditions or an area of unmet clinical need (EMA 2017a).

Most countries in Europe have regulations for both early access methods (Table 2). In EU member states, CUPs are implemented and developed at national level following Directive 2001/83/EC (EC 2001) in conjunction with Article 83 (1) of Regulation (EC) No. 726/2004 and guidance from the CHMP (EMA, n.d.-b).

As CUPs are implemented at national level and their organization varies between member states. A study from 2016 reported 18 out of the 28 EU member states have well-defined national regulations in place for CUPs (Balasubramanian et al. 2016). The French temporary utilisation programme, (the Authorization for Temporary Use (ATU)), is recognized as one of the clearest, most transparent, and most efficient programs in Europe (De Cock, Kolochavina, and Isherwood 2019). In contrast to programmes such as the Early Access to Medicines Scheme in the UK, the Temporary Authorization for Use in Spain and the Compassionate Use Programme in Italy, which are all based on manufacturer's free of charge "donations" of medicinal products, the ATU remunerates manufacturers and allows prices to be set freely (De Cock et al. 2019). As of October 2019, the French ATU had 19 cohort and 144 nominative ATUs active in comparison to 19 cohort CUP in Germany, 38 cohort CUP in Italy, and 75 promising innovative medicine (PIM) designations and 27 early access to medicines scheme (EAMS) scientific opinions in the UK (De Cock et al. 2019).

An article on the UK experience with EAMS highlights uncertainties on whether the scheme has achieved early patient access (Brazil 2020). Following the introduction of EAMS in 2014, concerns were raised by a commercial review in 2016 as to whether EAMS would be able to contribute to the achievement of timely patient access (PwC 2016), but no further evidence to that initial conclusion was found. Concerns were raised around the logistics of the scheme with evidence showing long processes from the moment a product was granted a PIM designation to the publication of a positive scientific opinion (Brazil 2020). Another issue raised about the scheme was that the timeframe of 12 to 18 months for a product to become available in the market is expected to take the time of an EMA marketing authorization application into consideration, which in practice usually takes longer (Brazil 2020).

Key findings

- The MA process is recognized to be a factor influencing market access timelines.
- The EMA MA application process is longer than the comparable FDA process, suggesting that EMA MA processes are driven by more and longer clock-stops during the review process and accompanied by longer timelines to receive the EMA's expert advisory opinion and a final decision by the European Commission (EC) after a positive opinion by the CHMP.
- Supplementary to standard pathways, pathways such as CMA, AEC and accelerated MA are implemented across the European Union to facilitate market access. Accelerated MA is associated with shorter review times, while CMA and AEC are recognized to enable access to medicinal products by granting approval prior to a complete marketing application or in cases where access would not have been otherwise granted due to limited and/or uncertain clinical evidence.
- Additionally, schemes facilitating early dialogue, parallel scientific advice, and parallel review on a national and multinational level are implemented in Europe to ensure an efficient MA process.
- Horizon scanning and early scientific advice can facilitate access to medicines by enhancing the readiness of health care systems and promptness of HTA bodies in preparing for the assessment of new and upcoming technologies. However, there is still an unmet need for engaging all the required and relevant stakeholders at these stages.

Table 2: Compassionate use programmes in Europe (EU27, Serbia and the UK)

	Named-patient basis	Cohort access	Authority for compassionate use programs
Austria	✓	✓	Austrian Federal Office for Safety in Health Care (BASG)
Belgium	✓	✓	Federal Agency for Medicines and Health Products (FAMHP)
Bulgaria	✓	✓	Ministry of Health
Croatia	✓	✓	Ministry of Health and Agency for Medicinal Products and Medical Devices of Croatia (HALMED)
Czech Republic	✓	✓	State Institute for Drug Control (SÚKL)
Denmark	✓	✓ ¹	Danish Medicines Agency (DKMA) (Lægemiddelstyrelsen)
Estonia	✓	✓	State Agency of Medicines (SAM)
Finland	✓	✓	Finnish Medicines Agency (Fimea)
France	✓	✓	French Agency for the Safety of Health Products (ANSM)
Germany	✓	✓	German Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich Institute (PEI)
Greece	✓	✓	National Organization for Medicines (EOF)
Hungary	✓	✓	National Institute of Pharmacy and Nutrition (OGYÉI)
Ireland	✓	x ²	Health Products Regulatory Authority (HPRA)
Italy	✓	✓	Italian Medicines Agency (AIFA)
Latvia	-	✓	State Agency of Medicines of Latvia
Lithuania	³	³	State Medicines Control Agency
Luxembourg	x	x	Division of Pharmacy and Medicines (Ministry of Health)
Malta	✓	✓	Malta Medicines Authority
Netherlands	✓	✓	Medicines Evaluation Board
Poland	x ⁴	x	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal	✓	✓	National Authority for Medicines and Health Products (INFARMED)
Republic of Cyprus	✓	✓	Cyprus Medicines Verification Organisation (CyMVO)
Romania	x	✓	National Agency for Medicines and Medical Devices (NAMMD)
Serbia	✓	✓	Medicines and Medical Devices Agency
Slovakia	✓	✓	State Institute for Drug Control
Slovenia	✓	✓	Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP)
Spain	✓	✓	Spanish Agency of Medicines and Health Products (AEMPS)
Sweden	✓	✓	Swedish Medical Product Agency (Läkemedelsverket)
UK	✓	✓	Medicines and Healthcare Products Regulatory Agency (MHRA)
Key:	‘✓’ indicates the availability and ‘x’ indicates no availability for the scheme in question.		
Source:	The Authors from secondary sources.		
Notes:	<p>¹ Under special conditions after application, the sale or dispensing of medicinal products in limited amounts (not covered by marketing authorization or not marketed in Denmark) may be authorized.</p> <p>² Currently, there is no provision in Irish legislation for the approval of compassionate use programmes for specific groups of patients with an unmet medical need.</p> <p>³ Currently, no special regulations for compassionate use programmes exist. However, in practice, compassionate use programmes are used in Lithuania by healthcare institutions, physicians, and pharmaceutical companies.</p> <p>⁴ Regardless of the provisions of the Pharmaceutical Act, the Minister of Health may issue a decision approving the use of an unregistered medicinal product in certain cases and/or within a compassionate use programme in individual cases justified by a threat to the patient's health or life.</p>		

Pricing

Once medicines have been granted MA and they are made available in national markets across Europe, prices are one of a range of factors contributing to the varying levels of access to medicines observed, especially in light of remaining uncertainty about effectiveness and overall costs, impacting both budgetary sustainability and patient access (EC 2020; Persson and Jönsson 2016). Therefore, the design and implementation of pricing policies should balance value, price and ability to pay in order to improve availability and reduce delays. A significant number of EU countries have low uptake rates for new innovative cancer drugs; the relative price of an innovative cancer drug will be higher in countries with lower income, both in consideration of affordability and in relation to other resources used in the healthcare system (Persson and Jönsson 2016). Pricing policies should also be considered in light of industry pricing strategies, as these may cause debate particularly for cancer drugs (Martinalbo et al. 2016). The WHO reports that there is evidence across various countries in Africa, Europe, the East-Mediterranean, Latin America, South-East Asia, and the Western-Pacific showing that 'current pricing policies (or the lack thereof) have led to considerable variability' in the prices of oncology medicines within and across countries (WHO 2018)¹².

External reference pricing (ERP) is used for the pricing of in-patent (and sometimes off-patent or generic), products in most European countries, apart from Sweden, which uses value-based pricing¹³ (VBP¹⁴), and the UK, which relies on rate of return regulation through the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS, previously the Pharmaceutical Pricing Regulation Scheme (PPRS)) (Holtorf et al. 2019; Rémuzat et al. 2015; Vogler et al. 2017). In Denmark external reference pricing only applies in the hospital sector, and free pricing is in place for other sectors (Sharaf 2018; Vogler et al. 2008, 2017; Vogler, Paris, and Panteli 2018). Germany relies on free pricing for the first year after regulatory approval (Angelis et al. 2018; G-Ba n.d.). In both cases of free pricing in Denmark and Germany, the reimbursement system may indirectly influence prices of pharmaceuticals (Vogler et al. 2008). In some European countries, ERP is used as the main systematic criterion for pricing setting, while in other instances countries rely on other methods or criteria in addition to ERP (Gill et al. 2019; Rémuzat et al. 2015).

¹² This assessment is from a report which obtained information through a targeted literature review, case studies, quantitative analyses, expert advisory groups, and a Member State information system. However, it is not clear whether this assessment reflects only on list prices or also on, as is often the case in many countries, confidential prices agreed between manufacturers and payors.

¹³ The Swedish TLV predominately assesses outpatient medicines, while in-patient medicines are assessed at county and provider level with advice or input from TLV.

¹⁴ VBP is a pricing system which determines the price of a drug based on the 'value' the product adds to society, where value is determined based on a range of criteria.

This section covers the impact of pricing policies in place in Europe across issues related to time delays, policy procedures and implementation, evidentiary requirements, company and distributor strategies, and overall policy outcomes.

Timelines and time delays

ERP. Evidence on ERP suggests these regulations may contribute to time delays in market and patient access. Notably, lower income Eastern and Southern European countries with stricter ERP regulations tend to have longer delays than Western and Northern European countries with higher GDP per capita and more affluent markets, which may be related to time-consuming bureaucratic processes between companies and governments when reaching price agreements (Kanavos et al. 2017).

VBP. Generally, the VBP system in Sweden seeks to encourage faster patient access by relying on ex-ante VBP assessment¹⁵ as a form of risk sharing to speed up reimbursement and uptake of effective new drugs despite uncertainties; manufacturers often generate additional health economic evidence on cost-effectiveness as part of these arrangements (Persson, Willis, and Ödegaard 2010). This structure is in place to avoid alternative processes which may delay reimbursement decisions until satisfactory evidence is available (Persson et al. 2010). Delays may result when applications for reimbursement are rejected, which could occur if submitted prices are too high and the product does not fulfil accompanying decision criteria, such as cost-effectiveness (Pontén, Rönholm, and Skiöld 2017). In these instances, the company may decide to apply again and submit another price, enter into negotiations with regional and Dental and Pharmaceutical Benefits Agency (TLV) representatives, or market the drug without reimbursement at national level, allowing regional councils to decide whether to cover the cost (Appelgren and Swarting 2020; Persson 2012; Pontén et al. 2017).

Policy procedures and implementation

The administrative burden of a given pricing policy may create a resource-intensive system, which could have an impact on affordability and/or accessibility.

ERP. While an ideal ERP system would be an administratively simple process (Kanavos et al. 2017), the administrative burden of ERP can vary to large degrees depending on the system's design. Across Europe some countries have transparent, well-established ERP processes (e.g. Austria and Portugal), while other countries are reported to have reduced transparency in their ERP system (e.g. Estonia) (Kanavos et al. 2017). Decisions on the number of countries in the ERP basket, the selection of reference countries, as well as implementation of the system,

¹⁵ TLV implements ex-ante and ex-post evaluations. Ex-ante evaluations are for new products where evaluation occurs before marketing starts, with decisions made in three to four months. Ex-post evaluations are conducted for the medicines already on the market prior to the introduction of new pricing arrangements in 2002.

including price revision arrangements, can have a significant impact on pharmaceutical prices, market entry and patient access (Houy and Jelovac 2013; WHO 2013). For example, the Greek ERP system has been reported to result in interrupted patient access due to issues with the implementation of ERP due to the size of the basket which includes 22 countries (EFPIA 2016). The variation in the design of an ERP system may have further unintended effects: for example, countries referencing the lowest price in their ERP basket might experience product shortages due to discontinuations and parallel export (Rémuzat et al. 2015). Amending certain characteristics of ERP methodologies in line with evidence could decrease medicine prices (Vogler, Schneider, and Lepuschütz 2020).

VBP. Similarly, VBP assessments can have high administrative burdens, notably for arrangements which require additional monitoring and pharmacovigilance (Deloitte 2012) and due to the resource-intensive nature of value assessments, and the time taken for discussions on value between authorities and manufacturers (Vogler et al. 2017). Potential bureaucratic challenges related to value metric assessment requirements could delay the release of new pharmaceuticals (Deloitte 2012). VBP in Sweden has also raised issues of regional variation in access to innovative products: budgetary responsibility lies with county councils in Sweden, who may lack the expertise in the complex models used by TLV to recognize the full value of novel treatments (Persson 2012). For example, lapatinib and bevacizumab were covered by some regional healthcare providers despite TLV not awarding reimbursement (Persson 2012).

Novel pricing mechanisms. It is also important to note systems may need to adapt to the different requirements posed by novel products and clinical developments. One of these relate to the pricing of combination therapies; few OECD countries have methods for the pricing of combination therapies for oncology, including France and the United Kingdom, where purchasers decide their willingness to pay based on the outcome of HTA value assessment and then negotiate prices with manufacturers with resulting price adjustments often taking the form of confidential rebates on list prices (OECD, 2020).

Evidentiary requirements

The time delays observed in the market access process across European countries may in part be due to requirements for the creation and submission of evidence. For systems with (extensive) evidentiary requirements, any potential impact of these on overall decision-making may be mitigated through addressing key issues: for example, the design of ERP systems may benefit from improvements such as addressing issues related to the accessibility of sources for pricing data used for the referencing process (Kanavos et al. 2017).

ERP may also contribute to delays in securing access for medicines in some settings as evidence requirements may be required to show prices in other settings: for example, pricing of a new

pharmaceutical product cannot occur in Greece if this exact product has not been priced in at least three other EU member states already (Bailey 2019; Government Gazette of the Hellenic Republic. 2019; Kalavrezou and Jin 2021).

Company and distributor strategy

Launch sequencing and launch delays. ERP creates the potential for companies to create strategies for the sequencing of product launches, 'used to delay or avoid launching new drugs in countries with potential lower prices, especially if they are small markets referenced by countries with larger markets' (Rémuzat et al. 2015).

ERP has been described as a policy that contributes to access and affordability problems due to the potential for the pharmaceutical industry to either select in which countries their products are launched (or not) or to delay launches in certain countries, given that manufacturers usually have a monopoly on sales for in-patent products (OECD, 2008).

The use of ERP as a policy may create circumstances in which manufacturers are less willing to launch in countries where ERP is implemented due to the impact of ERP on price levels and are more likely to launch innovative pharmaceuticals in countries with more freedom to set entry prices (Fontrier et al. 2019). As ERP is inherently a system relying on countries referencing each other, the pharmaceutical industry may be incentivized to introduce a product in a country where higher prices can be obtained, while delaying product launches in countries with relatively lower prices to avoid lower prices cascading down through reference pricing (Kanavos et al. 2017). This means the design of an ERP system, particularly which countries are referenced and how many, can encourage companies to launch products in a particular sequence; for example, if a country references drug prices in much lower income countries where the ability to pay high prices is low, companies will be encouraged to launch medicines in high price countries first (EFPIA 2020b). Therefore, launch sequencing and delays have international implications, with the possible effect of limiting access to and availability of pharmaceuticals in smaller countries, or countries with lower price levels, stricter price regulations, or design features which require them to wait for other countries to decide on a price or on reimbursement (Fontrier et al. 2019). The widespread use of ERP may also lead to circular pricing – the more countries used as reference countries, the less clear it is which countries' prices are the reference – which may also contribute to the potential for the strategic launch of a product (Rémuzat et al. 2015). Launch delays and/or the decision of a pharmaceutical company to not launch a product in a specific country can be influenced by potential global profits and manufacturer strategies for a specific products, together with other factors such as ERP, the disposable income in a country, the regulatory environment, parallel trade, and local market size (Fontrier et al. 2019; KPMG 2020).

The mean time to availability for oncology pharmaceuticals is 723 days in Portugal and 724 days in the Czech Republic, compared to 121 and 136 days in Germany and Denmark, respectively¹⁶ (IQVIA 2021). This is potentially due to a number of factors including the presence of ERP, parallel trade, and the size of the local market (Russo et al. 2010). Some countries with lower prices or lower market volumes tend to have fewer available products and longer delays in new product launches (Vogler et al. 2017); this implies that countries with a lower ability to pay wait longer for the introduction of new medicines (Vintura 2020b; Vogler et al. 2017). Additionally, evidence from Belgium shows some pharmaceutical companies delayed dossier submissions in order to circumvent receiving the Belgian price, usually in the low EU range (Toumi et al. 2014).

A simulation exercise showed that if ERP was eliminated, delays observed in Eastern Europe would fall by up to 14 months per drug (63%) on average¹⁷ (Maini and Pammolli 2017). The findings also suggest that delaying entry in some Eastern European countries yields higher revenue for 70% of drugs while withholding a product from all Eastern European countries is preferable to launching everywhere at the same time in approximately 20% of cases. The study also concludes no drugs would earn higher revenue by delaying entry in countries outside Eastern Europe. It is suggested that findings would result from the modelled scenario as in the absence of ERP the optimal strategy becomes to launch in all countries as soon as possible (Maini and Pammolli 2017).

It is important to note, however, difficulties in ascertaining the extent to which launch sequencing is delaying launches in certain countries: prices are often based on multiple criteria which companies cannot directly influence (Toumi et al. 2014). Additionally, the launch of a new product may also be dependent on other factors such as 'country income level, country market size, launch sequencing by the manufacturers and other pricing regulations and bureaucratic processes implemented along with ERP' (Kanavos et al. 2017).

Parallel trade. Parallel trade in medicines is the movement of a pharmaceutical product from a country where it is legally available to another country (Posado 2019). This phenomenon takes advantage of differences in price between the two countries – purchasing for a lower price and reselling for a higher price. Manufacturers may respond to this by strategically launching products (Kanavos et al. 2017), as the setting of a low price for a new product in a given market could lead to parallel trade (Rémuzat et al. 2015). This may lead to spill-over effects from low price to higher price countries and, through these effects, ERP and parallel trade may undermine patient access in EU countries (Kanavos et al. 2017). EU member states seem to be more exposed to spillover effects from ERP than non-EU countries due to the existence of parallel

¹⁶ Countries selected for their heavy reliance on ERP.

¹⁷ The study notes that the complete removal of ERP may not be feasible. Alternative options have been proposed in this study and elsewhere, such as payments to firms to forgo strategic delays.

trade among the EU countries, most of which implement some form of ERP to determine pharmaceutical prices (Fontrier et al. 2019). Parallel trade has an impact on availability in lower-priced countries; evidence exists in European countries to link product shortages to parallel exports, among other issues such as discontinuations (Kanavos et al. 2020; Pauwels et al. 2015). Countries such as the Czech Republic, Greece, Poland, Slovakia and Spain, more susceptible to parallel trade because of their low prices, resulting in drug shortages due to products being moved to high-price markets (Melck 2012; Ramos Diogo 2017; Zaprutko et al. 2020). Evidence shows similar effects in Italy: lower prices in Italy encouraged parallel trade from Italy to other countries, which in turn reduces local availability and product diffusion (Kanavos et al. 2020). Some countries, such as Portugal, have been developing measures to address parallel trade and resulting product shortages (Ramos Diogo 2017).

Others have argued that parallel imports improve access to drugs by making products available to consumers with lower purchasing power (Iravani, Mamani, and Nategh 2020).

Policy outcomes

This section considers two policy outcomes – cost-containment and resulting price levels – to provide an indication of the impact of pricing policies on affordability for the commissioner of services and for the patient.

Cost-containment. ERP has sometimes been seen to generate substantial savings for public purchasers, though this depends on the ERP methodology applied and the economic conditions existing in the country and across its reference countries (Kanavos et al. 2017). The context in which ERP is used may also affect what its impact will be: ERP may be a reasonable tool to inform price-setting or pricing negotiations but may be limited if the outcome is used as a fixed price or if it is used in conjunction with other pricing methods, such as VBP. True cost-containment is difficult within the pricing system of ERP as comparing pharmaceutical prices across countries is challenging, net prices are not available, irregular price reviews may mean price reductions in a referenced country do not necessarily result in corresponding price decreases in the referring country, the remaining potential for company strategies and launch sequencing, and circular pricing (Carone, Schwierz, and Xavier 2012).

The Swedish VBP system prioritizes decisions on the basis of equity, need and solidarity, while cost-effectiveness is seen as a supportive component in decision-making (Persson 2012). Within that, the TLV uses ex-ante and ex-post evaluations to aid with cost-containment. Evidence on the Swedish system suggests that pharmaceutical expenditure has decreased since the use of VBP (Persson 2012). Additionally, the Swedish system looks to contain costs through generic substitution to create the budgetary space to reimbursing novel, effective medicines (Persson 2012).

Price levels. Evidence on price levels resulting from the various pricing mechanisms used in the study countries is mixed. ERP has been linked to reduced pharmaceutical prices in some European countries (Kanavos et al. 2017; Leopold et al. 2012; Vogler et al. 2020). The majority of countries experience affordability issues at least in some therapeutic classes (Kanavos et al. 2019). The design of ERP policies may encourage higher prices in low-income countries, undermining the affordability of pharmaceuticals in these countries. However, questions have been raised whether ERP has a noticeable impact on price levels, and whether it results in competitive price levels when compared to other, more dynamic pricing systems which reflect therapeutic value (Kanavos et al. 2017). Spillover effects due to ERP may also lead to the transfer of price cuts in one country to another (Fontrier et al. 2019).

In Sweden, the VBP system takes therapeutic value into account. Even so, arguments have been made both ways: some say VBP has led to high pharmaceutical prices in Sweden, while others find VBP does not result in high pharmaceutical prices if a society's willingness to pay is recognized (Persson 2012). 2010 data showed Swedish price levels were slightly below average compared to other European countries (Brekke and Holmas 2012), while TLV found the Swedish price index has fallen in relation to other countries since 2014 (TLV 2018). Additionally, TLV implemented a rule in 2014 to cut pharmaceutical prices by up to 7.5% for products which have been on the market for 15 or more years and with little generic competition (Deloitte 2019).

Free pricing can drive prices to high levels, as manufacturers can set prices directly and price competition may be limited (Sharaf, 2018). Both Germany and Denmark address these issues. Germany allows free pricing in the first year after regulatory approval, as products are instantaneously available on the market after market authorization is granted (Angelis et al. 2018) at a price set by the manufacturer. After this year, the Gemeinsamer Bundesausschuss (G-BA) reviews the product in light of therapeutic value added; if no clinical benefit over the appropriate comparator is found, the product will be included in a reference price cluster system with medicines of similar pharmacological and/or therapeutic properties, or, where clinical benefit is proven, prices are negotiated with manufacturers (Angelis et al. 2018; G-Ba n.d.). Similarly, if clustering is not possible for a medicine with no added clinical benefit, prices are negotiated in the same way as medicines with added benefit (OECD 2018).

The review G-BA performs in light of therapeutic value added is suggested to have a main impact on prices (Martinalbo et al. 2016). The Danish Medicines Agency sets a limit on the number of medicine packages that each manufacturer can provide based on the cheapest reimbursable drug. This measure contributes to the Danish system offering some of the lowest-priced generic drugs in Europe to patients (Sharaf, 2018).

In the UK, the PPRS/VPAS is an indirect profit control tool within which manufacturers can set and modulate prices across their offering to the National Health Service (NHS) as they wish. The

Department of Health reports that UK prices set through the PPRS were either higher or comparable to comparator countries from 1999 to 2006 (Department of Health 1999, 2000, 2001, 2002, 2003, 2005, 2006, 2009). High pharmaceutical prices in the United Kingdom may be linked to other countries often using it as a reference country (Mrazek and Mossialos 2004). The PPRS was criticized by the UK Office for Fair Trading as the scheme may not encourage pricing based on therapeutic value, which the Office noted may mean the NHS cannot allocate available resources in the most efficient manner which may suggest implications for patient access and quality of care (Office for Fair Trading 2007). The VPAS, currently in place, has provisions for the closer alignment between pricing and value: in cases where manufacturers are unable to set a list price which falls within the cost-effectiveness threshold set by NICE guidelines, the Scheme has allowances for simple confidential discounts and the potential for patient access schemes and other commercial arrangements (Department of Health & Social Care and The Association of the British Pharmaceutical Industry 2018).

Key findings

- Evidence on ERP suggests stricter pricing regulations, such as ERP, may contribute to time delays in market and patient access.
- There is evidence on the impact of specific administrative aspects of pricing processes on access; this relates to both ERP and VBP. ERP design and implementation can have significant impact on pharmaceutical prices and patient access; VBP assessments, on the other hand, can have high administrative burden due to their resource-intensive nature and the time taken for discussions on value between competent authorities and manufacturers.
- ERP creates the potential for companies to create launch sequencing strategies, though it is difficult to ascertain the extent to which launch sequencing actually delays launches.
- There is mixed evidence on how pricing regulations impact price levels and contribute to cost-containment depending on the methodology and the mechanisms followed for price setting, the economic conditions in the referencing country and in reference countries in cases of ERP, and on other supply-side and demand-side policies implemented used to regulate prices and demand.

Health technology assessment

HTA is widely used as a value assessment tool aiming to inform decision-making and facilitate resource allocation using evidence-based review processes. The purpose of HTA is to systematically evaluate the properties and effects of health technologies, addressing their direct and intended effects, as well as their indirect and unintended consequences. The uptake of HTA in Europe has been very fast since the mid-1990s, aiming to guide rational healthcare decision-making and practice (Akehrst et al. 2017; Angelis et al. 2018). Differences in national HTA procedures, purchaser strategies and public administrations underscore respective differences in the structure, function, remit, and approaches of HTA bodies, which vary according to the health systems and political structures they operate in (EUPATI 2021). Diversity in HTA types and procedures across EU constitutes a challenge for companies to achieve market access. This is particularly so in EU member states with underdeveloped or not firmly established HTA systems and processes and can lead to a disconnect between HTA outcomes and patient access to new health technologies (EC 2016). Even though HTA can help purchasers and commissioners of services to decide on whether to reimburse a medicine or not, HTA processes create delays and challenges for access due to long evaluation processes, and variation in practices and funding recommendations across HTA bodies because of different policy procedures and implementation and evidentiary requirements (Ades et al. 2014).

This section identifies whether HTA processes contribute to patient access delays. Evidence is presented for both independent and integrated HTA bodies by considering key endpoints which can impede or facilitate timely access.

Timelines and time delays

Three main metrics related to HTA processes can be used to describe the availability of new medicines in markets and whether patients have access: a) time to market access, b) time needed by HTA agencies to assess the evidence submitted by the manufacturer, and c) time required for HTA assessment to be incorporated into funding decisions.

Time to market access. Time to market access refers to the average number of days between marketing authorization and a positive HTA recommendation (Vintura 2020b). According to analysis by IQVIA (2020) on time to market access, the average time difference between countries which ensure access to patients first, compared to those which ensure access last, is about 2.5 years (Vintura 2020b). Denmark ranks the highest with an average of 86 days, compared to Latvia and Poland which were ranked last with averages of 981 days and 891 days respectively (Vintura 2020b). For oncology medicines, evidence showed that variations in HTA procedures have an impact on the time it takes for new medicines to reach the market when

looking at the average time between MA and funding decision and thus factual availability for the patients (Bergmann et al. 2014).

Differences in the time to market access have been observed due to variations in the timing of HTA processes. Depending on the rules and procedures across settings, HTA processes can commence prior to MA in some cases (e.g., in England for oncology products), while elsewhere HTAs cannot commence until MA has been granted. Additionally, a few countries rely on HTA referencing, and as such, HTAs do not start until HTA recommendations are published in other reference countries; this is the case in Bulgaria, where manufacturers can submit their dossier to undergo HTA when a positive recommendation has been issued by the UK, France, Germany or Sweden (Malinowski et al. 2020). Finally, some differences existed in the time-to-HTA submission following MA: median times varied from 7 days in England, to 23 days in Italy, 29 days in France, and up to 42 days in Germany and 49 days in Spain (Wang et al. 2020).

Length of time of HTA process. The time to review the evidence once manufacturers submit their dossier for assessment by the HTA body is amongst the reasons why variations in access as well as delays are observed across countries (Angelis et al. 2018; Şaylan and Dokuyucu 2018). Based on a sample of 12 selected products mean times between MA approval and HTA recommendation vary significantly: Spain takes the longest to make an HTA recommendation (713 days), followed by Italy and Poland (504 and 462 days respectively), while France arrives at HTA recommendations in 227 days (Akehurst et al. 2017). Variations were further observed in the timelines for assessing the same product across countries (Akehurst et al. 2017). To speed up patient access to cost-effective new treatments, NICE in England has introduced a fast-track assessment pathway for medicines which have a base case incremental cost-effectiveness ratio (ICER) of less than £10,000 per Quality Adjusted Life Years (QALY) gained. HTA recommendations are made three to four weeks following dossier submission (LSE 2020).

Time of HTA recommendation uptake. Time delays related to HTA can be observed due to the delayed uptake and diffusion of HTA recommendations in reimbursement decisions. A significant lag in access can be created if HTAs are not completed in a timely manner. There seems to be a trade-off between fast access to new medicines and a well-performed HTA report (Ades et al. 2014). According to the EU Transparency Directive (EC 1998), EU member states should reach a decision on pricing and reimbursement within a maximum of 180 days after submitting their application to the competent authority of the national health insurance system (Angelis et al. 2018). In countries where HTA decisions should be issued prior to the availability of a medicine, such as in France (excluding medicines available through ATU), Italy and Spain, access can be delayed up to a year on average due to the time required for HTA decisions to be translated in reimbursement decisions (Akehurst et al. 2017). However, in Italy, for medicines of exceptional therapeutic and/or societal benefit and orphan drugs, reimbursement decisions

should not exceed 100 days (Martinalbo et al. 2016). In France, pricing and reimbursement decisions follow HTA recommendations which assess the added clinical benefit of a treatment (Martinalbo et al. 2016). In Germany medicines are immediately available once they have been granted a marketing authorization (Akehurst et al. 2017; Martinalbo et al. 2016). However, within three months of market launch, all newly introduced pharmaceuticals are evaluated based on their added benefit over a comparator under the Early Benefit Assessment (Fischer, Heisser, and Stargardt 2016). If an added benefit is proven, manufacturers negotiate with the Federal Association of Sickness Funds within another six months. If a clinical benefit is not proven, the medicine is priced based on reference pricing (Fischer et al. 2016). In England, medicine uptake depends heavily on NICE evaluations, as medicines become available for use after a positive recommendation (Ades et al. 2014; Martinalbo et al. 2016). In the Netherlands and Portugal time to access after a positive HTA decision faces further delays as negotiations on net price and inclusion of the assessed therapies into hospital level formularies take place at a later stage (Vintura 2020b).

Non-independent HTA systems. Non-independent HTA systems might contribute to unnecessary delays in funding negotiations due to unclear or non-transparent links and interactions with other institutions involved. In Greece, the fact that the HTA and the Negotiation Committees are not independent bodies, and their assessments rely on a pool of experts assigned by the MoH or the purchaser (the National Organization for the Provision of Health Services (EOPYY)); this undermines transparency, clarity and efficiency of the assessment and negotiation processes. The lack of transparent procedures and tools to be used for negotiations has been reported to be able to have a significant impact on timely reimbursement negotiations (Kanavos, Tzouma, et al. 2019); for example, negative recommendation decisions issued by the national HTA Committee are not directly communicated to manufacturers but instead, manufacturers are informed only in the case of a positive assessment in order to proceed to the negotiation process. If this does not happen following a certain period (i.e., 180 days), then a rejection is implied. Additionally, as negative recommendations are not published but are only implied, it is unclear when manufacturers can proceed with a re-submission. Nevertheless, encouraging clarity and commitment on the timelines between non-independent HTA systems and Negotiation Committees can help avoid these unnecessary delays in the process (Kanavos, Tzouma, et al. 2019).

European joint efforts. At European level, common efforts targeting access delays, such as supporting cross-country collaboration for the implementation of HTA, have taken place since 2002. In 2005, EUnetHTA was set up aiming to support cooperation between EU HTA bodies (Şaylan and Dokuyucu 2018). EUnetHTA piloted seven joint assessments¹⁸ of pharmaceuticals

¹⁸ Joint assessments conducted between 5 to 22 partners in the network.

between 2010 and 2016 following a rapid relative effectiveness assessment (REA) process developed by the network; the pilot assessments were close to operating at optimal timelines, suggesting the potential impact and useability of the joint assessments were increasing (Kristensen et al. 2017; Şaylan and Dokuyucu 2018).

In 2016, the European Commission presented suggestions on ways to strengthen EU cooperation beyond 2020. EU member states will continue to exercise control over appraisals and coverage recommendations, but clinical value assessments could be performed through some form of collaborative arrangement (Angelis et al. 2018; Kolotourou, Ermacora, and Grosvenor 2019). Collaboration on such assessments aims to ensure equitable and timely access to treatments across all EU member states and to further contribute to the harmonisation of processes and methods leading to economies of scale and greater transparency (Kolotourou et al. 2019). Following up on these suggestions and with an objective of facilitating market access, avoiding duplication of work for national HTA bodies and creating sustainable HTA cooperation across member states, the European Commission published a proposal for a regulation on health technology assessment in 2018, amending the previous directive (EC 2018b). The proposal suggests joint work focuses mainly on clinical assessments, scientific consultations, identification of emerging health technologies and voluntary cooperation across member states on issues other than HTA such as methods for the use of real world evidence, assessment of innovative technologies such as e-health and assessment of non-clinical domains such as the potential impact of technologies on the organisation of care (European Commission 2018). A political agreement about the HTA regulation was reached between the European Parliament and Council in July 2021 and will come into force gradually in three years. The agreement will replace the current system based on the 2018 proposal. It promises to improve availability of innovative health technologies by implementing a framework for joint work on clinical assessment and scientific consultations at a voluntary basis. This initiative aims to simplify submissions for manufacturers which will now take place at European level (EC 2021). Whilst this initiative is a step to the right direction, further clarifications and guidance are urgently needed to establish on how to assess clinical value, how the quality of the submitted evidence is evaluated, how RWE can be generated and used in joint assessments and establish joint ways for interpretation of clinical assessment (Kanavos, Angelis, and Drummond 2019). Access delays to new and innovative technologies could be caused by joint scientific consultations in the form of early dialogue if not all the EU member states are not in agreement on the evidentiary requirements when data are likely to be immature (Kanavos, Angelis, et al. 2019). Despite the joint efforts, data on epidemiology and local needs as well as budget impact analysis and price negotiations will always be needed and performed by local HTA authorities which will eventually add additional steps at the HTA process (Kanavos, Angelis, et al. 2019). In addition, should HTA outcomes at EU level be made binding, the result could be the addition of a further criterion based on EU-

wide recommendations for national reimbursement decisions, leading to potential further delays in patient access. These delays could be due to longer HTA review timelines, the involvement of multiple stakeholders and member states, and potential divergence of HTA recommendations at national and EU level if EU-wide recommendations fail to account for country-specific expectations and specificities (Kolotourou et al. 2019). Despite these common efforts, the European Parliament reported that delays between MA and reimbursement decisions, unavailability of medicines and inequalities of access among EU countries and regions remain (Şaylan and Dokuyucu 2018).

Evidence assessment across HTA systems

Inconsistent rules in HTA methodologies and procedures across HTA systems, such as differences in acceptance of indirect comparisons and real-world evidence, use of surrogate endpoints, selection of comparator therapy, and the level of stakeholder involvement in the HTA process among many others, can translate into divergent HTA outcomes for the same pharmaceutical across agencies, which may affect patient access to new technologies (e.g., delays and restricted access). Importantly, they also result in duplication of work and high costs for both HTA bodies and sponsors of technology, decreasing market predictability, and even affecting research and development (R&D) and investment in innovation negatively (EC 2016).

HTAs at national, regional and hospital level

Differences in HTA processes in European countries resulting in variability in methodological frameworks and decentralized decisions have been shown to contribute to inequitable patient access to new and innovative medicines (Akehurst et al. 2017; EFPIA 2020b; Martinalbo et al. 2016).

In some HTA systems assessments take place at several (national, regional and provider (hospital)) levels, as seen in Italy, Spain and Sweden. Systems with such complexities may result in divergent funding recommendations/decisions, and thus access to some medicines, due to differences in both the methodologies used to assess technologies and the selection of technologies undergoing assessment across these levels (Akehurst et al. 2017; EFPIA 2020b; Martinalbo et al. 2016; Tafuri et al. 2016). For example, evidence showed that the multi-level structure of HTA in Italy resulted in increased inequality of access to new medical technologies (Ciani, Tarricone, and Torbica 2012).

Nevertheless, HTA made solely at national level may not reflect local needs efficiently (Şaylan and Dokuyucu 2018). Evidence showed that long assessment timelines and the selected technologies subject for review by national HTA bodies may impede access to new and expensive technologies, which can be medically or economically critical at regional and hospital level (Şaylan and Dokuyucu 2018) given that decisions informed by HTA processes at these levels

determine access and availability (Martinalbo et al. 2016). However, to reduce patient access delays, manufacturers should be encouraged to generate evidence based on setting-based criteria and economic models which are acceptable with commissioners of services at different levels (Şaylan and Dokuyucu 2018). To be able to harmonize the cooperation across multiple layers of HTA, different regions should play different roles contributing to similar health outcomes for their patients, rather than different authorities duplicating efforts and encouraging inefficient practices, eventually resulting in unequal access to healthcare service provision (Ciani, Tarricone, and Torbica 2012). Although, there is still limited know-how and lack of transferability of results in hospital based HTA which can cause duplication of effort and restrict clinicians' independence in decision-making (Şaylan and Dokuyucu 2018).

Conditional HTA recommendations

HTA assessment outcomes can limit access to medicines for some populations or specific indications. For instance, many EU countries apply population restrictions as the relationship between clinical benefits and costs of certain medications only favours these specific sub-groups. For instance, in England, restrictions at HTA level can apply to cases where the technology is indicated only for second-line treatment (and beyond), or only for specific sub-populations, and to the need for specialist supervision or treatment monitoring (Angelis et al. 2018). In Poland, the same is observed when conditions are applied to positive recommendations restricting use to specific subpopulations or requesting monitoring when the medicine under assessment is used in clinical practice (Angelis et al. 2018).

HTA models

Variability in access to treatments is also attributed to HTA systems that make funding recommendations based on cost-effectiveness and those relying on relative clinical effectiveness (Martinalbo et al. 2016).

Stakeholder involvement in HTA assessment

The integration of stakeholders' perspectives during HTA processes is increasingly supported by systems in order to improve the policy and practical relevance of the process, enhance transparency and uptake of HTA and ultimately facilitate reimbursement decisions. Nevertheless, the extent to which these interested parties are included in the HTA process and subsequent decision-making differs significantly across systems. The type and scope of HTA also determines the feasibility, extent and respective impact that multi-stakeholder involvement can have in the HTA decision-making process with few systems offering formal mechanisms for participation (Sorenson et al. 2008; Wilsdon, Fiz, and Haderi 2011). On that front, it has been reported that in HTA systems that are not sufficiently independent, decisions might not be supported owing to

perceptions that the process was driven by a particular agenda, most often associated with purchasers or industry (Sorenson et al. 2008). Additionally, successful and efficient stakeholder engagement as well as efficient collaboration between different pricing/reimbursement decision-making authorities within a country (where applicable) necessitates enhanced transparency of HTA processes and clarification of the role of HTA in the subsequent national pricing and reimbursement steps (EC 2016). In England, the incorporation of patient perspectives during the HTA process showed that patient experience with safety and quality-of-life issues may carry an important weight on HTA outcomes when there is poor or lack of evidence on the clinical benefit against clinical outcomes for some advanced stage cancers (Chabot and Rocchi 2014). Inclusion of patient-reported outcomes (PROs) in HTA can influence HTA outcomes by focusing on benefits of technologies beyond their clinical- and cost-effectiveness. However, there seems to be a lack of a consensus among jurisdictions, regardless publication of local and international guidance, on how to generate robust PROs which are relevant to patients and on methods to statistically analyse and interpret these data (Böhme et al. 2021). Issues of generalisability and transferability of PROs across settings have been raised due to heterogeneity on the methods used for their generation and validation (Devlin, Lorgelly, and Herdman 2019)(Devlin et al 2019). Varying experiences with and confidence to PROs have been reported across HTA bodies, while evidence showed that PRO data can be more influential in oncology therapies compared to other therapeutic areas (Brogan et al. 2017).

Policy procedures and implementation

Clock stops during HTA processes can increase access delays: evidence showed that clock stops triggered by requests of additional evidence, or rejections during HTA processes can increase access delays (EC 2016; EFPIA 2020b).

Evidence requirements

Variation in access can be observed due to differences in the evidentiary requirements across HTA bodies for clinical and economic assessment and in the way these bodies perceive or interpret evidence. Different evidentiary requirements represent a challenge for manufacturers. This is because clinical evidence is usually developed at supranational level to capture the relevant population characteristics across a group of countries (i.e.: European level) and hence developing additional country specific evidence, which is usually in the form of observational studies, can be time-consuming. In addition, evidence requirements across countries are not always predictable or well-defined (EFPIA 2020b). Discrepancies also arise due to the way that HTA agencies deal with the associated uncertainties (Angelis et al. 2018; EFPIA 2020b). Variations in clinical evidence accepted across HTA bodies lie in patient populations, the comparator treatment used, trial design endpoints and statistical analysis (EC 2016; EFPIA

2020b). During the appraisal phase, HTA bodies evaluate the strength of the evidence submitted and make a scientific judgment on whether the evidence is robust and acceptable against the body's requirements (EC 2016; EFPIA 2020b). In Germany, France, and the Netherlands, uncertainty related to the evidence submitted is typically managed through requests for additional information; in France and the Netherlands these may include sensitivity analyses and additional clinical data which are associated usually with delays in market access (Akehrst et al. 2017). However, HTAs for oncology medicines and other related novel therapies are inherently challenging due to increased uncertainty related to their clinical efficacy that cannot be easily quantified at the time of launch due to immature data (Francois et al. 2019).

Differences in HTA outcomes across countries can be further attributed to additional dimensions of value such as rarity, unmet need and innovation that are considered in the appraisal process (Angelis et al. 2018). For instance, in Romania, the HTA system is mainly focused on costs rather than other additional value criteria creating challenges for patient access to innovative medicines (Kamusheva et al. 2018). By contrast, in England, a number of value and end-of-life criteria are considered explicitly in the assessment of most oncology medicines to ensure that HTA recommendations are considering other important social aspects beyond clinical- and cost-effectiveness (Chabot and Rocchi 2014). In addition, there has been an increase on the frequency at which innovation of technologies considered to play a substantial role in NICE's final deliberations on whether to accept higher willingness to pay thresholds. However, HTA committee's deliberations for various technologies differed in both the type and magnitude of innovation they considered as necessary for the technology to fulfil (Charlton and Rid 2019). In France, HAS recently launched an innovative medicines action plan to support and accelerate access to useful and safe innovations. The plan suggests ways to mitigate high clinical uncertainties related to these new technologies through conditional reimbursement and monitoring of real-world evidence. It further outlines two fast-track assessment procedures which allow early evaluation process and substantially reduce HTA timelines (HAS 2020).

Alignment on clinical assessment at European level would improve timelines to patient access, while European cooperation and alignment would also reduce duplication of efforts and allow for more efficient use of scarce human and financial resources (Vintura 2020b).

Real-world evidence and surrogate endpoints. Acceptance of real-world evidence (RWE) and use of surrogate endpoints is currently not harmonized across European HTA agencies. For instance, in Poland and Sweden the use of surrogate endpoints, excluding progression-free survival (PFS), is generally accepted when the clinical benefit of a treatment is assessed, while in the Netherlands and Portugal the use of surrogate endpoints is not widely accepted. England and Italy accepts surrogate endpoints on a case-by-case basis depending on the pharmaceutical undergoing assessment, the indication, and the surrogate endpoint used to prove clinical benefit

(EFPIA 2020b; Vintura 2020b). Evidence from England showed that very few cancer medicines were rejected due to clinical reasons, even though most of them did not provide evidence on the overall survival benefit (Chabot and Rocchi 2014).

Real-life data requirements such as generation of RWE derived from registries might also be one of the contributing factors for longer delays of access, as setting up registries can be time-consuming and bureaucratic (Şaylan and Dokuyucu 2018). Evidence from Bulgaria suggests that limited epidemiological data may pose an additional challenge to manufacturers for the preparation and submission of pharmacoeconomic and HTA dossiers beyond the lack of expertise for gathering data from real-world evidence (Kamusheva et al. 2018). Further, as clinical evidence is usually developed at global level, developing additional country specific evidence can be time consuming (EFPIA 2020b).

HTA recommendations and funding decisions

There is a variety of HTA systems across Europe, where full HTAs are being undertaken by independent agencies in some countries, while in others they are conducted by committees that are not independent to the relevant ministry's decision-making process and/or by external individual parties that have a clear budget interest in determining the final pricing/reimbursement outcomes (Wilsdon et al. 2011). According to a study looking at the most important obstacles and facilitators of HTA usage in decision-making in Europe, the most important challenge for access is the lack of an explicit framework on the way HTA evidence is used in the decision-making process, while the availability of an explicit framework is among the most important facilitators (Cheung et al. 2018). Therefore, differences in HTA systems inherently influence subsequent availability/unavailability of medicines. The many changes in HTA processes within jurisdictions over time and the consistent international variations in HTA practices indicate that different countries have different values, which can result in different preferences for reimbursement (e.g., automatic reimbursement at regulatory approval or a more closed system), and HTA systems have often been shaped by political and historic arguments (e.g., the UK Cancer Drugs Fund (CDF)) (R Vreman et al. 2020). As such, there are systems where recommendations by the HTA body are not always followed in subsequent reimbursement decisions, particularly where HTA is performed by a national agency but decisions are taken by regional bodies, while even assessments undertaken on an 'independent' HTA basis can also be affected by the overall political context in which they operate (Wilsdon et al. 2011). A study looking at the agreement between HTA recommendations and funding decisions for oncology medicines in Central and Eastern Europe showed that in Poland, contrary to Hungary and Latvia, there was a low level of agreement between HTA and funding. From the eleven cancer drugs (out of a total of thirty-six) with a positive HTA recommendation, two were not reimbursed, and

out of the twelve medicines with a negative HTA recommendation, five were reimbursed (Malinowski et al. 2020).

Additionally, HTA coverage recommendations are also influenced by different priorities in individual settings, different perception of benefit and value, and setting-specific preferences on additional 'social value judgements' beyond clinical benefit assessment and economic performance (Angelis et al. 2018).

Opportunities for product reassessments, additional evidence resubmissions and alternative pathways of funding exist for products that may have received a negative recommendation decision at the national level. Different reimbursement experiences have been observed across settings depending on the different modalities available across the different systems (see section 10.1).

HTA resubmission and re-assessment

HTA dossier resubmission and statutory processes for re-assessment can have an impact on the final HTA outcome, potentially alter previous negative recommendations and thus, enhance availability of medicines (R Vreman et al. 2020). Statutory re-assessment occurs at regular periods regardless of availability of new evidence to assess whether technologies should still be reimbursed or not, as is the case in Germany and France (LSE 2020). Resubmission of HTA dossiers by manufacturers is possible across HTA agencies when new evidence on safety, effectiveness and/or cost-effectiveness becomes available or when new evidence is generated as a part of a commercial access arrangement (see section 9)(LSE 2020). For example, clear requirements and guidance for resubmissions have been established in Scotland, where the Scottish Medicines Agency (SMC) offers pharmaceutical companies the option for a fast-track resubmission when the only change is a new or improved simple patient access scheme, accelerating re-assessment and reimbursement decision-making processes following a previous rejection. This process allows a resubmission to proceed directly to the SMC committee with an overall assessment timeline of up to 14 weeks, as long as it is received within three months of the date when the original SMC decision was issued to the company (Scottish Medicines Consortium 2020). Nevertheless, in non-independent HTA systems, such as in Greece, the lack of transparent re-submission timelines, may act as an unnecessary challenge, due to the limited time allowed for manufacturers to generate new or revise old evidence for resubmission purposes following a negative recommendation (Kanavos, Tzouma, et al. 2019).

Other initiatives facilitating market and patient access at HTA level

Early scientific advice at HTA level. Early scientific advice is a voluntary process which provides manufacturers with the opportunity to present and receive feedback from HTA agencies

on their evidence generation plans (LSE 2020). In Europe, many national HTA bodies, including NICE in England, Haute Autorité de Santé (HAS) in France, G-BA in Germany, and TLV in Sweden, have formal processes for early advice to manufacturers. The process usually involves submission of a product development plan briefing, a face-to-face meeting with the HTA agency and a panel of experts, and provision of an advice report with comprehensive responses to questions raised in the briefing (LSE 2020). Other HTA bodies such as AIFA in Italy, or regional HTA bodies in Spain offer scientific advice on an informal or ad hoc basis (Russo et al. 2010). According to the literature, even though early scientific advice aims to improve access delays by expediting the process of HTA assessments, there is still an unmet need for engaging all the required and relevant stakeholders including purchasers, clinicians, health service managers and patients (Husereau et al. 2016).

Key findings

- Differences in HTA systems and procedures (e.g. routine requests for economic analysis or budget impact), evidentiary requirements (such as acceptance of early phase clinical studies, use of RWE and surrogate endpoints and selection and acceptance of comparator therapy), willingness to pay thresholds, the way evidence is interpreted, and additional dimensions of value considered during assessment across EU member states contribute to variations in coverage decisions and to unequal availability of medicines across countries.
- Access delays due to HTA timelines can be attributed to (i) when an HTA process is initiated, i.e., in parallel to MA or after MA has been granted; (ii) the length of the HTA process itself, and; (iii) the time it takes for a positive HTA recommendation to be translated into a funding decision and for the latter to be implemented by the health care system.
- Positive HTA recommendations are not always translated in positive reimbursement decisions, particularly where HTA is performed by a national agency but decisions are taken at regional level. Differences in the level of agreement between HTA recommendations and funding decisions are further varying across countries.
- Stakeholder involvement in the HTA process can contribute to better access to medicines by providing a more accurate assessment of the value of the technology, contextualising the evidence submitted to the relevant setting and aligning the needs of society. The type/scope of HTA determines the feasibility, extent and respective impact of stakeholder involvement and few systems offering formal mechanisms for participation.
- Many jurisdictions allow for resubmissions (e.g., England, Denmark, the Netherlands, Scotland) and have statutory reassessment procedures (e.g., France and Germany), which can alter previously negative decisions and thus, enhance availability of medicines.

Pricing and reimbursement negotiations

Pricing and reimbursement negotiations between purchasers/commissioners of care and manufacturers determine pharmaceutical transaction prices and are a key step in determining availability and affordability. This section aims to identify evidence on the challenges arising during negotiation processes by considering key endpoints which can impede or facilitate timely access. While this section presents evidence on negotiations to set up reimbursement prices, impact of main pricing policies used to determine list prices across Europe is presented in section 3.2.

Timelines and time delays

In some markets, there is immediate access after marketing authorization, at least for some products. For example, in Germany the standard process provides manufacturers with a temporary period of free pricing that enables access to a medicine that has been authorized by the EMA almost from day one, avoiding the delay resulting from an ongoing HTA assessment and pricing negotiations (EFPIA 2020b). Nevertheless, in other countries delaying factors exist, including the lack of adherence to national timelines and multiple layers of decision-making (Vintura 2020b). To address these issues, in England for example, evidence can be submitted prior to a positive CHMP opinion to allow the assessment and negotiation process steps to start as much as possible in advance. The fast-track procedure prioritises reimbursement applications which can be filled before the marketing authorisation is being granted. However, negotiation must be requested within 30 days after the marketing authorisation has been granted. Some countries, like Denmark, Italy, and Portugal, allow for pricing and reimbursement processes to commence after CHMP approval, with no need to wait for EMA or EC decisions (EFPIA 2020b; INFRAMED 2019; Medicinrådet 2021).

Additionally, where regional or local funding options exist, they may have a great impact on both the timing and the number of drugs available for patients from region to region within a country. This can be due to organizational factors, such as the use of regional/local/hospital formularies periodically updated by regional commissions. For example, the Italian model is characterized by a centralized National Health Service, responsible for drugs assessment, pricing, and reimbursement, but the regions act as the main budget holders and, therefore, are responsible for the local provision of healthcare. Especially before the introduction of the Innovation Fund mechanism at national level in 2017, the fragmented Italian system posed a significant challenge for patient access to new treatments because medicines often needed to undergo further approval processes which differ from one region to the other, or even within a single region across different health districts and hospitals (Prada et al. 2017). As such, it has been reported that the average time from national reimbursement decisions to the regional evaluations for

formulary inclusion could vary widely between regions (Visentin, Heiman, and Ripellino 2015). For example, reports suggest that, in the past, not all oncology products approved by AIFA were subsequently accessed by patients in every Italian region, with an average delay to patient access across regions of around five months (Russo et al. 2010). Nevertheless, the introduction of the Innovation Fund mechanism in Italy since can provide nationwide access to high-cost pharmaceuticals which are classified as 'highly innovative', through two dedicated funds of €500 million each for innovative oncology and non-oncology products respectively (see also section 10.1) (Flume et al. 2018). Similarly, Spain follows primarily a regional HTA approach, with 17 regions responsible for the management of their own health budgets. At the central level, once a medicine is licensed by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), the Ministerio de Sanidad, Consumo y Bienestar Social (MSC) decides on its reimbursement. Even though a positive recommendation by the MSC implies that the medicine is approved even for regional use, hospital specific budgets still remain limited, so their commissions often fund the medicine only when very specific clinical and cost criteria are met (Corbacho et al. 2020). On the contrary, an example of opportunity to secure local funding and access arises in England and Wales, where all decisions being made at the central level are also recognized in Wales and the NHS is obliged to ensure budget for local implementation in the cases of positive reimbursement decisions (Vintura 2020b).

Policy procedures and implementation

Clarity/transparency of national regulations

The lack of clearly defined and transparent administrative processes in pricing and reimbursement negotiations may have a negative impact on the ability and opportunity to conduct these negotiations across different markets. Additionally, the fragmented pharmaceutical sector within a country (i.e., different purchasers and/or different funding/negotiation mechanisms for the outpatient and inpatient sectors) considerably limits the bargaining power of public procurers, and subsequently disincentivizes the exploration of collaborative procurement strategies among purchasers across the sectors for the benefit of patients (Vogler et al. 2018).

Level of burden/workload associated with types of reimbursement

Representatives of the pharmaceutical industry have noted that the involvement of multiple national HTA and pricing/reimbursement agencies and authorities, many with slightly different application procedures and information requirements, significantly increases the negotiation workload due to their additional, more detailed requests (EC 2016). Consequently, reimbursement decisions and subsequent patient access to innovative therapies may be delayed

or not granted at all due to increased administrative burden that these negotiations are associated with in specific settings.

Multiple layers of reimbursement decision-making and number of stakeholders involved

At each stage of the HTA process, including deliberation and recommendation decision-making, stakeholders can contribute valuable insights as their perspectives and needs can highlight aspects that are not readily addressed through a technical assessment of the submitted evidence (Pichon-Riviere et al. 2017). Even though stakeholder involvement can facilitate recommendations that are produced as a result of an HTA, it may also have implications for access due to issues around the local adaptation and effective roll-out of recommendation decisions to affiliates, and the efficient translation of understanding to multiple stakeholders involved in local access negotiations (Alderson 2014).

Evidentiary requirements

Even though all countries assess similar types of evidence under HTA, the specific criteria or endpoints considered during the negotiation process, their level of weight/value towards the final recommendation decision, and the way they are incorporated (e.g., explicitly vs. implicitly) varies across countries, implying that access to the same medicines could vary considerably in individual countries. For example, while submission of high-quality evidence is necessary for the purposes of the HTA process, it is not sufficient to ensure that this will be reflected or considered in the reimbursement decision making process, such as in Denmark or France, where even though cost-effectiveness analysis is recommended in manufacturers' submissions, this is not often considered when determining reimbursement (Sorenson et al. 2008).

Key findings

- Some markets offer immediate access after marketing authorization at least for some products (e.g., Germany), but delaying factors exist in other countries (i.e., lack of adherence to national timelines, multiple layers of decision-making, implementation of ERP).
- Regional funding modalities may have an impact, both positive (e.g., England/Wales) and negative (e.g., Spain), on a) the availability of drugs and b) the time to availability across regions of a given country.
- The involvement of multiple national HTA and reimbursement authorities increases the negotiation workload due to additional evidentiary requests, with respective impact on access and time to access.
- Stakeholder involvement can facilitate HTA recommendations but simultaneously raises concerns around the efficient translation of understanding to multiple stakeholders involved in local access negotiations.

- Cross-country variation in the endpoints considered during the negotiation process, their level of weight and the way (e.g., explicit vs. implicit) they are incorporated in the final recommendation decision, translates into diverging access outcomes for the same medicine in different countries.

Commercial access agreements

The rapid progress of therapeutic innovation and the introduction of new therapies might be favourable from a patient perspective but poses challenges for policy-makers in managing the market entry of these high-cost medicines and maintaining their long-term affordability, especially under social health insurance (EC 2018a).

Specific challenges for policy-makers arise in the evaluation of the real-world value of these new therapies as the data available on the cost effectiveness of many new innovative medicines, especially in oncology, are severely lacking at the time of product launch (Piatkiewicz, Traulsen, and Holm-Larsen 2018). As these challenges can lead to delayed reimbursement decisions and patient access, manufacturers and purchasers are seeking ways to collaboratively manage the market entry of new pharmaceutical products, such that health expenditures that are growing particularly in the field of oncology are controlled (Gonçalves et al. 2018) while risks related to premature evidence are also mitigated; one way to achieve this has been through the introduction of contractual arrangements between the two parties, referred to as Managed Entry Agreements (MEAs) (Dabbous et al. 2020; Efthymiadou and Kanavos 2021). More broadly, these have also been described as managed access schemes, which generally aim to address access challenges, through achieving an optimal balance between uncertainty, price and fast access (Vintura 2020b).

Although it has been suggested that submissions with a proposed MEA do not guarantee a positive recommendation from HTA agencies, it is generally agreed that the increase in their use, especially for new oncology therapies, indicates that there is still a high likelihood of reimbursement as long as both parties share the financial risks while the company has time to demonstrate the real-world value of their product subject to an MEA (Piatkiewicz et al. 2018).

Current experience with the implementation of MEAs suggests that most of these schemes have been used in the reimbursement of oncology medicines, reportedly accounting for about 40% of all MEAs, and continue to be increasingly implemented in oncology (Efthymiadou and Kanavos 2021; Ferrario and Kanavos 2013; Gonçalves et al. 2018; Nazareth et al. 2017), while the use of outcomes based agreements specifically is predominant among oncology therapies (KPMG 2020; Nazareth et al. 2017)

Furthermore, in terms of their implementation, there is a wealth of information on how different MEA modalities aim to impact the availability of or access to medicines across the European countries. In Belgium, the specific objectives pursued by the introduction of MEAs were to provide patients access to promising, innovative therapies, while also providing an additional option for pharmaceutical companies to access the market (Ferrario and Kanavos 2013). In Portugal, Coverage with Evidence Development (CED) agreements provide the option for

temporary coverage, which can be extended or become permanent if the manufacturer provides additional data supporting the drug's effectiveness at the end of the 2-year conditional reimbursement period (Ferrario and Kanavos 2013). In Poland, MEAs have been introduced to limit public expenditure on drugs while extending the positive reimbursement list (Ferrario and Kanavos 2013). Additionally, limited time coverage restrictions have been observed in Poland, whereby earlier patient access to the new compound is granted while additional real-world data is collected (Wilsdon and Barron 2016). In Sweden, MEAs between Swedish health care purchasers (regions), the reimbursement authority TLV, and manufacturers were introduced in 2014 as a tool to facilitate timely and fair access to treatments for patients in different regions of the country (Andersson et al. 2020). In the United Kingdom, MEAs typically refer to "patient access schemes", which predominantly include discounts and free doses. Their main target is to facilitate or secure access through improvement of cost-effectiveness by bringing it to a value which is acceptable from a willingness to pay threshold and therefore, favourable towards a positive reimbursement decision (Ferrario and Kanavos 2015).

Finally, as these agreements allow the price of pharmaceutical products to be aligned with the respective benefit they provide even in a particular combination of products, different agreements may be implemented depending on the association of the combination medicines concerned, and therefore, they can be of extreme importance in enabling access to such combination therapies which are increasingly relevant in fields such as oncology and HIV/AIDS (Gonçalves et al. 2018).

Timelines and time delays

Evidence suggests that under the right conditions, MEAs can help manage budget impact, reduce uncertainty surrounding the evidence base of innovative medicines, and promote faster access to innovative therapies; "MEAs are used extensively across Europe, helping patients to get access to new innovative medicines at affordable prices, mostly in the form of straight discounts and price-volume agreements (PVAs)" (LSE 2020). For example, according to a study carried out in 2010 in Italy, the introduction of these agreements is reported to have contributed substantially to an improvement in Italian patients' access to oncology medicines (Gonçalves et al. 2018). Nevertheless, it has also been argued that MEAs might eventually prove counterproductive for extending patient access in the long term (Dabbous et al. 2020). For example, in Germany, sickness funds may refrain from using this type of agreements due to concerns that once the agreement expires and a number of patients have already started treatment, the manufacturer might either not be willing to continue providing the drug as part of the agreement or the conditions of it will become less favourable compared to when the drug was first introduced (Ferrario and Kanavos 2013).

Time invested in negotiations and re-evaluation of completed schemes

Country specific processes for MEA agreements determine whether an additional delay will occur, as, for example, lengthy or stalled negotiations automatically contribute to patient access delays. For example, it has been suggested that in England, the Patient Access Scheme Liaison Unit (PASLU) process delays submissions to NICE, while in others markets there is included flexibly in the negotiation with the result that this can eventually accelerate the process (LSE 2020), such as in Italy where the time to patient access for oncology products tends to be shorter if there is an agreement in place (Russo et al. 2010).

Additionally, the type of agreement in place and its respective negotiation process plays a role in determining timelines and potential time delays to patient access. For example, in the Italian setting, an analysis of all drugs with MEAs, primarily including oncology and orphan drugs, showed a national and regional time to market of 14.1 and 6.1 months respectively, with an increase to 16.4 and 7.2 months respectively following an outcomes-based MEA and a decrease of the national time to market to 11.5 months following a financial based agreement (Urbinati, Rova, and Mantuano 2017).

Time delays due to country specific risk sharing negotiation process characteristics have also been reported in Germany, where the G-BA may proceed to time-limited resolutions (TLR) as a form of coverage with evidence development (CED) to address uncertainty surrounding health technologies at the time of market launch. In 2017 alone, 14 (29%) of the 49 drugs that were assessed were subject to TLRs lasting from six months to seven years, with an average of 2.5 years (Dabbous et al. 2020). Similarly, in Portugal, CED agreements offer conditional coverage for a period of two years, after which the drug's therapeutic added value and cost-effectiveness must be re-evaluated and coverage decision updated accordingly, overall adding to the negotiation process (Ferrario and Kanavos 2013).

Shorter timelines can be observed in Belgian MEA negotiations, where a final recommendation decision is made on the 150th day and in cases of a negative decision, manufacturers can apply for reimbursement through an MEA, or the purchaser may suggest reimbursement through an MEA issued by the Minister. In any case, the time clock is stopped and a 120-day negotiation process between the manufacturer, the pharmaceutical industry board, health insurers, the National Institute for Health and Disability Insurance (NIHDI), the Minister of Social Affairs and the Minister of Budget starts (Ferrario and Kanavos 2013).

Delays in data collection for outcomes-based schemes

Although post-marketing data collection and surveillance is a crucial component for the successful implementation of outcomes-based contracts, the process introduces significant

burden for manufacturers, national systems and the time to patient access (LSE 2020). For example, pay for performance schemes may make it difficult to measure outcomes in curative therapies due to the time lag between administration and apparent clinical benefit, while in general, it is hard to establish and reliably measure effectiveness due to changes over time in clinical practice.

Similarly, CED schemes offer the opportunity for patient access to new medical products during development. However, access may be terminated following the expiry of a CED scheme, while national CED research can be redundant and costly considering the requirements for international research by manufacturers and the need to perform extra studies to prove cost effectiveness (R. Vreman et al. 2020).

Nevertheless, existing challenges in the tracking of outcomes across diseases for which longer data collection periods are required, such as disease progression following oncology therapy, can be addressed from a few perspectives by including strict follow-up requirements, aligned financial terms of the contract, and sometimes automated data collection solutions (KPMG 2020).

Policy procedures and implementation

Despite the fact that the application of MEA is heterogenous across European countries and often associated with high transaction costs and administrative efforts, MEAs can still contribute to accessibility at the level of individual countries by allowing patient access to drugs that would not be reimbursed otherwise (Pauwels et al. 2017). However, contextual differences around data collection infrastructure and supply chain of specialty medicines influence the feasibility of applying different types of MEAs across countries or between regions/territories within countries (Pauwels et al. 2017).

Specific concerns related to administrative burdens have also been raised around outcomes-based agreements, as they are complex, and many countries still do not have experience with outcomes-based MEAs or have the administrative infrastructure to facilitate their implementation (Bouvy, Sapede, and Garner 2018). First, the process of negotiation for outcomes-based agreements can be challenging and time consuming, as is the collection of additional evidence and the future monitoring and re-evaluation of the product, if required, while issues around obtaining alignment in expectations/interpretation of collected data and data coverage requirements between regulators and purchasers remain (Bentata et al. 2020; Kanavos and Mills 2015; Wilsdon and Barron 2016). Second, performance or outcomes-based schemes are associated with high complexity in collecting required data. Consequently, further difficulties and delays may arise from engaging clinicians and hospital pharmacists to conduct additional administrative tasks to collect data as they see this as an additional burden (Wilsdon and Barron 2016). For example, in Italy, while monitoring registries have been acknowledged for informing

AIFA and other stakeholders about the performance of new products, they have also been criticized for creating a significant data collection burden for health professionals and provider organisations (Wenzl and Chapman 2019; Wilsdon and Barron 2016).

Additionally, the confidential environment in which all types of MEAs operate may pose challenges on their efficient implementation (Wenzl and Chapman 2019). The confidentiality requirements of these arrangements may limit the opportunity for some stakeholders to learn about and engage in MEA negotiations therefore discouraging their widespread adoption as a policy tool across countries (Ferrario and Kanavos 2013; World Bank 2018). Nevertheless, an increase in MEA transparency, particularly around the negotiated prices/discounts, could lead to misuse of MEAs with potential access implications, especially in low- and middle-income countries. More specifically, it has been argued that, in order to circumvent price transparency requirements, markets may increasingly attempt to use complicated outcomes-based contracts to achieve more favourable ex-post discounts. As such, markets with a lack of experience in more sophisticated contracts could be disadvantaged by this misuse of MEAs since they will not have the same capabilities to achieve the same level of discounts (Bentata et al. 2020).

Evidentiary requirements

Real World Evidence

Real-world data in the context of MEAs aims to develop evidence of real-world value (and costs) in a structured and comprehensive way to ultimately, minimize the evidentiary gaps for the purposes of novel payment models that involve performance-based reimbursement. However, evidence suggests that difficulties may exist in the appropriate interpretation of this new data collected by the different stakeholders involved in the evaluation of this evidence which respectively impedes the development of appropriate coverage decisions that are based on analysis/interpretation of this data (Bouvy et al. 2018; Wenzl and Chapman 2019). For example, a Dutch evaluation of an outcomes-based MEA for a stage III colon cancer treatment collected additional data through a patient registry and found that patient heterogeneity made it problematic to eventually provide accurate evidence on the incremental cost-effectiveness of the treatment using the collected data (Bouvy et al. 2018). Furthermore, collecting additional data for payer purposes often represents an additional administrative burden for clinicians and healthcare professionals and remains a challenge especially in cases where infrastructure and data collection mechanisms are underdeveloped (Wilsdon and Barron 2016).

Of course, despite these challenges, the requirement for collection of real-world performance data under outcomes-based contracts, can have a positive impact on coverage and availability of medicines, provided that the expected response/outcomes have been met. For example, In Portugal, CED agreements not only provide an option for temporary coverage during a two-year

conditional reimbursement period, but also upon submission of additional, favourable effectiveness/cost-effectiveness data, permanent coverage can be secured (Ferrario and Kanavos 2013).

Key findings

- Although MEAs do not guarantee a positive reimbursement recommendation, their extensive use across Europe has contributed substantially to improvements in market access, specifically for oncology medicines which account for about 40% of all MEAs.
- MEAs can be of extreme importance in enabling access to combination therapies, which are increasingly relevant in oncology and HIV/AIDS.
- MEAs are generally considered positive for enhancing patient access, although in some cases the expiry of these agreements might eventually prove counterproductive for extending patient access in the long term, unless the terms of the agreement are renewed.
- Country-specific processes for MEA agreements, the type of agreement and the associated negotiation process may determine if access delays will occur; for example, the PASLU process in England may delay submissions to NICE, while in Italy outcomes-based MEAs seem to reduce national/ regional time-to-access).
- The process of post-marketing data collection and surveillance is essential for the successful implementation of outcomes-based MEAs but it may introduce significant burden on manufacturers and national health systems and may delay access to patients, especially in cases where coverage does not occur until the necessary real world data has been collected.
- The confidential nature of MEAs may pose a challenge for efficient implementation but increased transparency on the negotiated discounts could encourage markets to use complicated outcomes-based contracts to achieve more favourable ex-post discounts, with potential access implications for countries that do not have the capacity or experience to achieve the same level of discounts.

Institutional funding mechanisms

Type of arrangements and circumstances

HTA rejections or limited clinical evidence often create significant challenges to accessing a specific treatment at the national level. Nevertheless, specialized funding mechanisms can play a role in leveraging diverse funding sources to overcome such obstacles. For example, in cases where a medicine for seriously ill patients (such as patients with cancer or other life-threatening diseases) is not accessible and reimbursed by the national health system of a country, alternative coverage options in the form of budgets, special or earmarked funds, and special purchasing processes exist (LSE 2020). Several types of specialized funds have been established across various European countries, aiming to address gaps in coverage from different HTA systems and reimbursement processes and provide alternatives to established reimbursement rules, with the ultimate goal of securing access to high-cost medicines that would otherwise be unavailable (LSE 2020; Vogler et al. 2018). Nevertheless, an important challenge to their successful implementation relates to their associated risk of overspending and more important the risk of blocking access for patients if overspending is prohibited (R. Vreman et al. 2020).

One of the most notable examples of managed access funds in Europe is the new, post-2016, CDF in England. If a promising drug with evidentiary uncertainties is recommended for observation in the CDF, more time to collect evidence about how well it works is provided, allowing for evidence gaps to be closed while interim funding from CDF is secured and until permanent reimbursement can be granted (LSE 2020; Vintura 2020b; Vogler et al. 2018). Comparable mechanisms exist in other settings and for specific types of products (e.g., specialized funds for orphan and ultra-orphan medicines in Belgium and Scotland respectively) (LSE 2020). Similarly, the Italian Innovation Fund (see section 8.1) was introduced in 2017 to incentivize access to innovative medicines (Vastesaegeer 2018) and enable faster patient access by removing budgetary restrictions at the regional level (Flume et al. 2018). Under this funding mechanism, medicines are assessed for their innovative nature based on the therapeutic need, the added therapeutic value, and the quality of clinical evidence (Flume et al. 2018; Fortinguerra et al. 2020; Mammarella and Tafuri 2018). If a medicinal product is granted "full innovativeness" status for a specific therapeutic indication, its manufacturer can access two dedicated yearly funds of €500 million Euros each, depending on the type of medicine (one fund for oncology, the other for all other innovative medicinal products). Alternatively, the product can be granted the status of "conditional innovativeness" which allows immediate access to all regional formularies with no additional re-assessments at the local level (Mammarella and Tafuri 2018).

Reviews aimed at adapting and updating funding mechanisms

While creating a separate fund for medicines that would be otherwise not available through standard reimbursement mechanisms may improve coverage, concerns have been expressed that institutional funding mechanisms introduce equity risks by funding medicines that may eventually prove cost-ineffective while displacing funds from more cost-effective health care interventions (LSE 2020). However, evaluating the experience of existing initiatives such as the CDF in England, or the Italian innovation funds, could help avoid inefficiencies and unnecessary pitfalls arising from specialized funding mechanisms (Vogler et al. 2018).

Policy procedures and implementation

Evidence on the impact of these schemes is limited, although it has been reported that they often carry high administrative burden, whereas it has also been highlighted that the presence of earmarked drug funds may signify that the underlying HTA system is failing, subsequently raising issues around equity (LSE 2020). For example, critics argue that prioritizing oncology drug expenditure with the “old”, pre-2016, CDF in England, deprived investment in the whole cancer management pathway and reportedly, between 2010 and 2016, it consumed the equivalent of the annual NHS’ expenditure on oncology drugs, all while not collecting the appropriate data (Dabbous et al. 2020).

Key findings

- Several types of specialized funds exist across Europe that enable access to high-cost medicines that might otherwise not be reimbursed through standard reimbursement processes.
- The post-2016 CDF in England allows for evidence gaps to be addressed while interim funding is secured and until permanent reimbursement can be granted.
- The Innovation Fund in Italy has facilitated access to innovative medicines and enabled faster patient access by removing budgetary restrictions at regional level, through two dedicated funds for highly innovative oncology and non-oncology drugs respectively.
- While institutional funding mechanisms can enhance patient access to medicines, they should be designed and implemented with caution to avoid funding cost-ineffective drugs, while displacing funds that would provide access to more cost-effective health care interventions. For example, by prioritizing oncology drug expenditure, the pre-2016 CDF in England deprived investment in the whole cancer management pathway.

New funding models

As innovative technologies are increasingly developed for a range of different patient populations and across different diseases, challenges are introduced for the current pricing and reimbursement systems which are not directly designed to differentiate the value that a product provides across settings and therapeutic areas. In an effort to overcome these challenges, novel payment models between purchasers and manufacturers have been discussed which typically aim to link reimbursement levels to real-world performance or use of a product and align product funding with actual patient value received (LSE 2020). These novel funding models can broadly refer to i) contracting/over-time models, ii) portfolio agreements and iv) re-insurance models.

Outcomes

Contracting models typically aim to spread costs over time, through innovative financial agreements that allow purchasers to control budget impact over the long term (i.e., amortization, instalments and annuities) (Kanavos 2020). For example, over-time models (alternatively known as high-cost drug mortgages), instalment payments, annuity payments or staggered payment models decouple payments for a treatment from delivery of the medicine. This allows a purchaser to secure funding through spreading the costs of high-cost therapies, including cancer, Hepatitis C and cell/gene therapies, over the time in which benefit is accrued (Garrison et al. 2019).

Amortization mechanisms per se cannot define the 'right price' of new treatments but, when combined with performance-based agreements, they can potentially help align the long-term costs and economic benefits of treatments, allowing purchasers to cover innovative therapies while remaining within their budgets (Vogler et al. 2018).

More comprehensive models involve multiple years with payments spread over time based on achievement of pre-specified performance criteria (Kanavos 2020). Multi-Year Multi Indication (MYMI) agreements can accelerate access to medicines, bringing significant benefits to patients particularly in countries that would otherwise assess each indication: a process that is resource intensive and delays patient access (Wilsdon et al. 2019). These models help purchasers to manage the challenges of affordability and provide the incentive for companies to register indications. For example, in Belgium, 5,000 patients became eligible for access to immunotherapy for the lung cancer indication as a result of MYMI agreements, with significant benefits in terms of saved lives (Wilsdon et al. 2019). However, it is also clear that MYMI agreements are not the only approach to providing timely patient access to oncology therapies and experiences with alternative approaches (e.g., England's CDF or the immediate access offered in Germany) should also be examined (Wilsdon et al. 2019).

Portfolio agreements refer to a model whereby for each purchaser that wants to buy medicines, the manufacturer negotiates the overall number of treatments bought, allowing the supply of multiple treatments to individual purchasers. For example, in 2018, NICE deemed that the cost-effectiveness and budget impact of an innovative therapy for cystic fibrosis (CF) did not justify its respective high price. In response to that decision, the manufacturer offered NHS England a 'portfolio-based' deal, covering all its CF drugs, including those yet to be approved. This deal aimed to secure one price for all future CF treatments, as well as improved access and budget certainties (NHS England 2019; Rawson 2018).

Finally, reinsurance and stop-loss policies whereby insurance providers purchase reinsurance or stop-loss from another insurance company, are discussed as a possible option for financing high-cost curative therapies by transferring the financial risk of these therapies to the reinsurance company which pools risk over a larger scale (Kanavos 2020).

Timelines and time delays

Time invested in negotiations and re-evaluation of completed schemes

Experience with MYMI agreements in Belgium, Denmark and the Netherlands has demonstrated their potential to minimize significantly the time taken for reimbursement approval of medicines with multiple indications (Bentley 2018). For example, the mean time to patient access was reduced by 365 days in Belgium and 100 days in the Netherlands (Lawlor et al. 2021). These agreements ensure faster and broader patient access by reducing the administrative burden associated with conducting the same upfront evaluation process for each indication of the same product, while aligning price to the value that the product offers for each indication without the need for indication-based pricing (Lawlor et al. 2021).

Nevertheless, country specific legal arrangements are also required for the introduction of MYMI agreements which can contribute to unnecessary delays in the negotiation process. For example, in Belgium, while the required legal adjustments are minor, it has been reported that these schemes can still take time to be agreed on and implemented (Wilsdon et al. 2019). Similarly, in the Netherlands, even though the Ministry of Health is familiar with the implementation of MYMI agreements, negotiation processes are specific to each company's product and as such, the negotiation timeline for each new product's MYMI agreement has been reported to remain lengthy (Wilsdon et al. 2019).

Additionally, another example of stalled negotiations and their impact on access delays arises from the CF portfolio-agreement negotiations in England: this approach was met with substantial criticism as the discussions reportedly took four years to complete, introducing significant distress for patients awaiting access (Parsons 2019).

Policy procedures and implementation

Challenges in the uptake of novel payment models are likely to vary by type of model and the country in question. However, lack of capacity and established legal or regulatory framework to facilitate adoption of such mechanisms across healthcare systems may hinder the implementation of innovative funding models (EFPIA 2020a; IQVIA 2019b). Payments over time may introduce affordability issues, while rigidities in the current pricing and reimbursement mechanisms may impede adaptation to new data and uptake of innovative funding models that would otherwise have the potential to facilitate access to treatments (LSE 2020).

Evidentiary requirements

Novel solutions to evidence in new funding models are used in some countries. Belgium has sought to solve challenges in the reimbursement of multiple indication immuno-oncology treatments through the development of MYMI agreements. To review the performance of such agreements including the utilisation of these treatments and patient outcomes, an electronic health record (EHR) system was implemented to connect health care professionals and to share health information. The utilisation of this EHR system in combination with the MYMI agreement it supports has resulted in faster access for a broad patient population to innovative multi-indication immuno-oncology treatments (MSD 2017). Similarly, the Drug Rediscovery Protocol (DRUP) in the Netherlands provides an alternative data generation and reimbursement pathway for oncology precision drugs targeting small populations. An outcomes-based agreement which gathers evidence is implemented to identify activity for off-label therapies and, in cases where activity has been demonstrated, positive reimbursement can be achieved (Vintura 2020b).

Key findings

- Contracting payment models allow purchasers to secure funding and access through spreading the costs of high-cost therapies, including oncology and gene therapies, over the time in which benefit is accrued.
- MYMI agreements in Belgium, Denmark and the Netherlands have significantly minimized the time taken for reimbursement approval of medicines with multiple indications.
- Rigidities in current pricing and reimbursement mechanisms and lack of capacity and established legal or regulatory frameworks may impede adaptation to new data and uptake of innovative funding models that would otherwise have the potential to facilitate access to treatments.

Market uptake and diffusion

Whilst the majority of issues related to access to medicines tend to focus on delays to marketing authorization, pricing, negotiation, and reimbursement policies as discussed in previous sections, there are issues after these traditional 'market access' stages that can significantly impact the time it takes for patients to access the right medicines. The specific country environment influences commercial decisions and, in some markets, even if a product is reimbursed and available within the country it is not used in the market in practice (EFPIA 2020b).

Medicine accessibility encompasses the ability to obtain a prescription for the medicines as well as factors related to the traditional market access stages (OECD 2020): once reimbursement has occurred, innovations still need to be correctly prescribed to the patients they are intended for, who must be able to use them in the way in which they have been designed. In order for this to happen the following must occur (Vintura 2020b):

- Administration – finalisation of administrative procedures and allocation of budget
- Integration – adequate health system infrastructure and clinical care pathways
- Prescription – prescriber awareness
- Use – patient access to the right expertise (i.e., geographical, financial and awareness)

Critical factors for the uptake and utilisation of new medicines include issues such as impact and influence of drug and therapeutic committees (DTCs), cost of new medicines to hospitals, including potential budgets, and any discounts, plus pharmaceutical and patient pressures (Godman et al. 2018). This section focuses on post market-access presence and diffusion and factors considered include those related to variations in medicines purchasing, for example, formulary, direct-to-hospital (or pharmacy), clawbacks and rebates; supply chain challenges related to the manufacturer, wholesaler and pharmacy; and finally issues related to dissemination to patients and patient uptake which can be impacted by the speed with which clinical guidelines are updated to include novel medicines, the mandatory nature of any clinical guidelines, prescription rates, co-payment requirements and geographic factors.

Impact of purchasing and procurement agreements

Procurement. Most healthcare systems use a combination of public and private sector funding sources to purchase or procure medicines, where procurement is defined as the process of purchasing goods, works or services (e.g. medicines) through a formal process that may or may not involve a call for tenders (Vogler et al. 2018). The quality of this procurement process can impact patient access. If procurement is done in a predictable manner, it can benefit from economies of scale and price reductions whilst assuring medicine quality and reliability of supply.

Most country governments make purchases to ensure their citizens have efficient access to the medicines they need but governments in lower income countries tend to play a smaller role in procurement, making it harder for vulnerable citizens to access required medicines with many relying on government-sponsored programs for healthcare (IFPMA 2012). Cross-border efforts at joint procurement in the EU is expected to contribute to sustainable access to health technologies, though in the practical implementation of such initiatives, challenges remain (Espín et al. 2016). Several joint procurement efforts including joint purchasing, and joint negotiations for purchasing, and information sharing are currently in place in Europe: for innovative medicines, the BeNeLuxA, more recently known as the International Horizon Scanning Initiative (IHSI), the Nordic Pharmaceuticals Forum and the Southern European Initiative, and for pharmaceutical products more generally, the Baltic Partnership Agreement, the Romanian and Bulgarian Initiative, the Declaration of Sofia, and the Central Eastern European and South Eastern European Countries Initiatives. These efforts can promote availability of medicines through cross-border exchange of products in short supply and through mitigating overly high transaction costs by pooling skills, capacities and joint negotiations; this can be particularly relevant when purchasing for smaller populations, either for small countries or for rare conditions with a limited target patient population (Espín et al. 2016). However, to secure supply and foster meaningful innovation, joint procurement mechanisms need to be strategically designed to avoid opportunistic tendencies arising from the monopolistic power of some countries. For example, countries with capacities to achieve lower prices and privileged conditions of supply under confidential price agreements might not want to engage in joint purchasing initiatives to avoid potentially higher prices (Espín et al. 2016). Similarly, if one of the participating markets engages in parallel export activities, suppliers might avoid granting the low price they otherwise would have charged to some countries, for fear that the 'parallel exporter' might divert products to higher-priced markets (Espín et al. 2016).

Taxes and tariffs. As a result of taxes and tariffs on pharmaceuticals the cost of medicines can vary significantly across countries. Some of this may be due to production costs or preferential pricing offered to lower-income countries, situations involving high, unnecessary mark-ups (including taxes, tariffs, and additional charges by intermediaries) can increase the final price to significantly more than the manufacturers base price by up to 15%. These additional mark-ups can significantly hinder patient access, particularly for those in lower income countries. Evidence has shown that tariffs tend to be lowest in the richest and poorest countries and highest in those with intermediate income levels (IFPMA 2012).

The development of direct delivery to pharmacy from manufacturer models has seen the proportion of pharmacy sales originating from wholesalers increase to over 10% in Denmark,

Greece, Ireland, Luxembourg, the Netherlands and the UK, and over 20% in the Czech Republic, France and Italy (EP 2011).

Tendering. Tendering is based on formal and competitive procedure aiming to achieve lower prices by awarding contracts to the 'best' offer. In general, in Europe tendering is usually applied to the hospital sector, both at individual and group level, or via voluntary pooling of regional hospital procurement at the national level by procurement agencies. Shifts have been made towards the latter in several countries, including Denmark and Norway, resulting in efficiency gains and reduced prices (Vogler et al. 2018). Countries such as Germany, the Netherlands and Romania have shifted outpatient, off-patent purchasing to tender systems to enhance competition and reduce prices (Vogler et al. 2018).

Tender systems, and effective procurement in general, have been linked with reaching a larger patient market, particularly in the utilisation of generics. While generic substitution is in place in most European countries, biosimilar substitution is still met with resistance by some stakeholder groups, such as physicians, with implications for the prescribing and subsequent uptake of biosimilar products subject to tendering (Vogler and Schneider 2017).

Despite the benefits that could be achieved from cross-country collaboration in tendering (or in procurement more generally), differences in legal requirements and regulatory procedures pose a challenge in its successful implementation. There is also the possibility of a 'race to the bottom' of prices which could lead companies to withdraw from certain markets triggering medicine shortages and limiting patient access (Vogler et al. 2018). Furthermore, biosimilar tenders are primarily selected based on cost considerations with little available evidence around "value" added when awarding contracts (Dranitsaris et al. 2017; Simoens and Cheung 2020). As such, despite reported savings for public purchasers from biosimilars tendering in Italy and Norway, the uptake of these products may still be hampered due to "value" related concerns discouraging physicians and pharmacists from biosimilar substitution (Vogler and Schneider 2017).

Supply chain challenges

The pharmaceutical supply chain is the process by which prescription medicines are manufactured and delivered to the patient requiring them. It is a complex network of steps involving a wide range of suppliers including manufacturers, wholesale distributors and pharmacy benefit managers (McGrail 2020). A badly designed supply chain, plus additional issues such as counterfeiting, cold-chain shipping and supply chain visibility, can disrupt patient access and have negative effects on public health (KFF 2005).

A typical pharmaceutical supply chain will consist of one or more of the following (Shah 2004):

1. Primary manufacturing (which may include contractor sites)

2. Secondary manufacturing (which may include contractor sites)
3. Market warehouses / distribution centres
4. Wholesalers
5. Retailers / hospitals

Primary and secondary manufacturing sites are often geographically separate due to tax and transfer price optimisation, and there are often more secondary manufacturing sites, which take the active ingredient produced at the primary site and add excipient materials along with further processing and packaging, than primary ones, serving local and regional markets. In the UK wholesalers play a significant role with 80% of demand flowing through one of three main players and the remainder going direct to hospital (Shah 2004).

The Covid-19 pandemic has highlighted the vulnerability of the medical product supply chain. Restrictions on mobility of goods from the place of production to the place of consumption due to limits on cross-border flows or transportation issues, for example export bans, authorizations and restrictions on critical supplies or grounding of commercial flights can have an impact on patient access (Miller et al. 2020). Similarly, restrictions on quality and availability in specific markets, perhaps due to regulatory compliance failures, have led to multiple recalls of medicines, e.g., recalls of valsartan supplied by Zhejiang Huahai and heparin by Baxter Healthcare Corporation (Snodin and Elder 2019; Tanne 2008).

The pharmaceutical supply chain can significantly affect drug costs, which can have a knock-on effect on patient access. The price of drugs depends on several negotiations between wholesalers, pharmacies and purchasers and the margin taken by wholesalers and retailers can vary significantly across member states with government policies influencing the margins in place (EP 2011). Similarly, the costs of transportation, storage, staff salaries and stock losses factor into the final costs of medicines (IFPMA 2012). Whilst costs of distribution can be reduced when manufacturers sell directly to pharmacies, or work with a restricted number of wholesalers the impact of distribution method can be as high as 50% of a drug's retail price (IFPMA 2012). Markups can also inflate prices with wholesale markups ranging from 2% to 380% and retail markups ranging from 10% to 552% (IFPMA 2012). There may also be costs related to importation (for example, port charges and pre-shipment inspection) which are beyond the control of the manufacturer and can increase the costs of the product for the patient. The more simple a supply chain the fewer opportunities for 'middlemen' to add their own markups (IFPMA 2012).

National patterns for distribution vary greatly. For example, in Italy in 2011 there were 193 pharmaceutical wholesalers whilst Germany had only 16 and the UK had nine, with the top three wholesalers controlling 85% of the market (EP 2011). There are similar variations in the density

of retail distribution pharmacies. Whilst reducing the number of steps in the supply chain should make the process of delivering medicines to the patient more efficient there are still issues with medicines availability with the manufacturer's responsibilities for streamlining supplies and managing stock, plus the generally fragmented nature of medicine distribution leading to shortages in some markets. Similarly, lack of alignment in the different incentives and disincentives from each stakeholder's perspective (including the manufacturer, wholesaler, and retailer) can impact prices and availability. Exchange rate fluctuations have led to exacerbations of this issue in the UK in the past (EP 2011).

Patient uptake

Unfortunately, availability within a country does not necessarily equate access. The medicine's journey does not end when it arrives at the pharmacy or hospital and is on the public reimbursement list as it still needs to make its way to the patient, generally via a prescription. Whilst the Netherlands has a relatively short time span for reimbursement of oncology products (at 234 days after EU marketing authorization) only 20% of patients actually received the products in the year following reimbursement decisions (Vintura 2020b). This delay seems to be either due to the fact that, following national reimbursement decision-making, contracts need to be negotiated with individual hospitals within the context of individual budget constraints (which will be talked about in more detail in the next section), or due to the fact that the inclusion of new medicines within clinical guidelines can be delayed, even for Europe's five main cancer types (Vintura 2020b). Similar observations on budget constraints can be seen in Sweden: while local providers are required to follow TLV decisions, they can rely on influencing prescribing behaviour to limit use (Persson 2012). Access and uptake of in-patient treatments at county level in Sweden may vary as well: county councils cannot obtain discounts for outpatient products as TLV sets the retail price, however, as discounts are available for hospital medicines, county councils may tend to purchase the lowest priced product in a therapeutic class regardless of product profile or TLV evaluations (Persson 2012).

Clinical practice guidelines. Clinical practice guidelines (CPG) are information support tools, generally used to facilitate physician's clinical decisions on the appropriate treatment of a patient's medical condition and compliance with these guidelines can serve as a benchmark for appropriate health care (WHO 2015). Clinical guidelines are a key stage in the final step to the patient and without them, or with outdated guidelines that do not take into account novel products, physicians may limit their use of a new product due to lack of clarity in terms of its positioning in the existing treatment pathway (EFPIA 2020b).

There is significant variation across the EU in terms of speed with which new oncology products are included in the guidelines and many are not regularly updated to include latest innovative

therapies (Conge & Vernimmen, 2020). For example, in England it can take up to 34 months for inclusion in guidelines whereas Denmark can take as little as 10.8 months (EFPIA 2020b).

In fact, in 2020, Portugal was using guidelines last updated in either 2012 or 2013 for breast, colon and lung cancer (Vintura 2020b). As a result, their use will be limited as healthcare professionals tend to follow the available clinical guidelines.

Prescribing behaviour. Prescribing habits can also impact patient access and, perhaps unsurprisingly, are one of the most powerful predictors of new medicine uptake. The greater the number of prescriptions written within a country, either across all drugs or just for those within the therapeutic class of the new medicine, and the wider the prescribing portfolio, the greater the chance a physician has of writing a prescription for the new medicine. It has also been shown that high prescribing volumes in the therapeutic class of a new product may correlate with early adoption of the new medicine (Lublóy 2014). In Central and Eastern Europe patient access has been shown to be further restricted by volume limits on prescribing, for example, implicit volume restrictions (price volume agreements) and explicit ones (central tendering and volume limits for healthcare workers) (Izmirlieva 2014).

There are also instances where different countries take different approaches to value in class competitors. Some countries want physicians to have full access to all available products on the market to provide patients with the best options and to allow a certain amount of physician 'freedom' whilst others have chosen a preferred product in a class. The result is variation in the proportion of products available and with sales. In Greece for example, around 72% of available products have no sales – the medicine is on the reimbursement list but budgets are not allocated for use or it is not recommended - whilst in Spain, only 5% of the available products have no sales (EFPIA 2020b).

Geographic variation. Finally, geographic issues can impact patient access to novel medicines. For example, rural practice locations may result in later new drug adoption compared to urban environments as rural doctors have fewer opportunities for interactions with professional peers, which can be an important factor in the decision to initiate new treatments. Similarly, rural locations may be less likely to be visited by pharmaceutical sales representatives which can impact physician medicine usage (Lublóy 2014).

Key findings

- The quality of procurement processes can have an impact on patient access; efficient procurement can benefit from economies of scale and price reductions whilst assuring medicine quality and reliability of supply.
- Unnecessary mark-ups in taxes and additional charges by intermediaries can increase the final prices of pharmaceuticals and significantly hinder patient access.

- Tendering can reach a larger patient market, particularly for generics, but also introduces a 'race to the bottom' of prices which could lead companies to withdraw from certain markets triggering medicine shortages and limiting patient access.
- Rural locations may experience slower adoption of new drugs when compared to urban environments.
- Availability within a country does not always equate access. Impediments and delays to access may arise due to local/regional reimbursement decision-making requirements and budget constraints, and/or due to delayed adaptation of clinical guidelines and prescribing patterns with funding decisions.

Macro-level factors

Beyond the endogenous factors discussed so far, there are several exogenously determined, system-wide factors and imposed constraints that can have an impact on patient access to new medicines. The previous sections have discussed key focus elements that can be maximized and optimized to enhance access, but the exogenous macro factors cannot be manoeuvred in the same manner.

Macro-economic factors. There is significant variation in GDP per capita within Europe which varied from €5,410 (Serbia) to €81,000 (Luxembourg) across the region in 2020 (Eurostat 2021). There is also significant variation within the EU in terms of country spending on healthcare, affected, but not fully explained, by income levels, population age structures and epidemiological profiles (Darvas et al. 2018). The effect of economic factors on health and well-being has long been known and economic factors – broadly separated into seven categories¹⁹ – are consistently identified in local, national and international population health frameworks as both exercising influence on health and providing levers to improve health and reduce health inequalities (Naik et al. 2017). OECD data shows that absolute healthcare spend ranges from €1,300 per capita in Romania to €5,300 per capita in Germany and relative pharmaceutical expenditure as a percentage of overall GDP varies between 3.5 and 5 times between countries (Vintura 2020b). Countries with higher income tend to initiate suitable treatment earlier and ensure better access to new medicines for HIV/AIDS (Gokengin et al. 2018).

If insufficient budget is in place, access to medicines can be delayed or impeded. For example, in England, despite the NHS being required to fund products recommended for reimbursement by NICE via national NHS England and local Clinical Commissioning Groups (CCGs), there a degree of 'postcode' lottery still exists whereby local budget constraints prevent all members of the population having access to the same medicines (Vintura 2020b). Uptake of oncology medicines in seven cancer types across countries has been shown to vary with country economic status with usage in poorer countries being one third to half the uptake of the five largest EU member states (France, Germany, Italy, Spain and the UK) and wealthier countries (Hofmarcher et al. 2019). In both European and non-European countries, countries with lower GDP per capita had lower availability of oncology medicines or availability only with high associated out of pocket payments, an observation more dominant for higher cost oncology medicines (WHO, 2018). For HIV/AIDS, a connection between antiretroviral drug availability in Central and Eastern Europe and income has also been observed: the availability of many, particularly newer, antiretroviral

¹⁹ These include market regulation; institutions; money supply; finance and credit; balance between public, private and third sector; labour markets; production and consumption; and approaches to the economy

drugs tended to be significantly better in countries with a higher income status (Gokengin et al. 2018).

Health system characteristics. Differences in patient access to oncology medicines across countries may be the result of varying capacities of healthcare systems (i.e., administrative, technical, and financial), willingness to pay for oncology medicines and societal priorities regarding cancer care vis a vis other diseases (OECD 2020). Affordability for healthcare systems themselves will be influenced by government priority setting and resource allocation which is impacted by societal values and the priority afforded to health relative to other societal policy areas such as education and social welfare.

Access to medicines can be impacted by general health system performance and infrastructure. An effective healthcare system needs to ensure patients have access to high quality health facilities, diagnostic centres and healthcare workers and clinical pathways should facilitate the optimal use of novel medicines by ensuring timely detection and diagnosis via screening and acknowledgment of risk factors, coverage of appropriate biomarker testing, timely referral to centres of excellence if needed and absence of financial considerations with prescribers and patients when selecting therapy (Vintura 2020b). The general readiness or preparedness of a health system to adapt to and integrate new approaches can also have an impact on access to new medicines.

Resources and budget constraints at regional or hospital level can limit the use and uptake of novel products in clinical practice (Conge and Vernimmen 2020). Whilst most EU countries make coverage decisions at national level, some Nordic countries, Italy and Spain make decisions at regional or local level. Regions may have variable technical and/or financial capacity to respond to pressures that certain new medicines may pose to their systems which can impact patient access (OECD 2020).

Patients' socio-economic status and ability to pay. Affordability for the patient is reliant on the medicine being both covered and having acceptable levels of co-payments. The structure and overall burden of user charges have access implications, particularly if there are no age or disease-specific exemptions. Such situations can be particularly problematic for vulnerable groups not protected from high user charges for pharmaceuticals and if pharmaceuticals are exempt from annual caps on user charges. In Austria, for example, medicines fees of €6 per prescription are in place whilst in Estonia, the reimbursement system for prescription-only medicines is based on the category of the medicine with a 100%, 90%, 75% or 50% reimbursement rate (plus a basic co-payment of €2.50) based on the severity of the disease, the efficacy of the medication and the social status of the patient (Kringos et al. 2013). The impact of user charges can be disproportionately high for vulnerable groups, especially those groups which are poorer: the WHO has reported that households in the poorest quintiles are

more likely to experience catastrophic health expenditure²⁰, and that outpatient medicines are a key driver of catastrophic health spending (WHO and WB 2017).

The socioeconomic status of the patient can also impact physician prescribing behaviour, irrespective of consideration of medical need. For example, high income patients have been shown to be receiving new medicines earlier than others, partly due to their ability to pay out-of-pocket for these products (Lublóy 2014). Similarly, privately insured patients are more likely to received new medicines earlier than others (Lublóy 2014).

Burden of disease and epidemiology. Unmet medical need and disease burden has been shown to be considered the most important factor influencing the development of a successful medicine (Sendyona, Odeyemi, and Maman 2016).

Settings with higher rates of a specific disease may not offer access to appropriate treatment. In the WHO European region, HIV/AIDS cases reported in Eastern Europe accounted for 80% of the total new HIV diagnoses in 2016 (Gokengin et al. 2018). However, although antiretroviral therapy (ART) has been found to be offered free of charge in all countries in Central and Eastern Europe, newer first-line drugs with better tolerability and lower short- and long-term toxicity and those single-tablet regimes associated with better adherence seem to be less available (Gokengin et al. 2018).

The burden of disease may also play a factor in whether or not appropriate healthcare responses are implemented. For example, the growing number of HIV infections in many Eastern European countries stems from to limited access to ART and to harm-reduction services (e.g., needle and syringe programs, and opioid substitution therapy) (GBD 2017 HIV collaborators 2019).

Further context of a country and other healthcare system factors are also important: a study on Malta and Norway, selected for their similar prevalence of HIV (0.1%) but different incidence rates (14.5 per 100,000 in Malta and 4.2 per 100,000 in Norway), showed 19 antiretroviral drugs were available in Malta compared to 44 ART drugs in Norway (Namulindwa 2018). Both countries provide ART free of charge through their national health systems, but Norway displayed a higher willingness to pay and also provided pre-exposure prophylaxis (PrEP) than Malta (Namulindwa 2018). Particular issues raised for the Maltese context included an outdated formulary, limited HIV-specific funding, and issues with the forecasting of drugs (Namulindwa 2018). The way care and treatment and health policy are organized in a country often shape the overall access pathway and drug availability is one of several parameters which impact access overall.

Cultural, racial, and political issues. Recognition of the burden and unmet need of specific disease can be dictated in part by political and societal pressures.

²⁰ The WHO indicator on catastrophic expenditure is defined as "the proportion of population with large household expenditures on health as a share of total household expenditure or income" (WHO and WB 2017).

The specific value that a country places on a medicine and approaches to treatment may also vary between countries. For example, some countries may favour surgical rather than pharmacological interventions which can impact the degree to which a country considers themselves to have an unmet need which needs to be addressed (EFPIA 2020b).

Stigma around certain diseases may also play a large role in poorer health outcomes in some settings. A study of 48 EU and non-EU/EEA countries highlighted stigma and discrimination among health professionals and/or key populations, and language and culture, as potential challenges to ensuring those diagnosed with HIV are accessing treatments (ECDC 2017). The criminalisation of issues related to HIV-exposure, such as non-disclosure, drug use and sex work, may also impact access to or uptake of treatment (ECDC 2017).

Specific groups may also experience poorer outcomes: access to health care for Roma people is more limited than for non-Roma people (Ivanov 2004). This lack of access may be due to the attitudes of the healthcare provider related to social stigma such that patients from these populations are at risk of not getting coverage or care due to occasional or perceived discrimination (Palm et al. 2021). Alongside the Roma population those that are asylum seekers, trans-gender people, individuals with stigmatising illnesses such as HIV/AIDS and irregular residents have all been shown to experience healthcare-related discrimination across Europe (Palm et al. 2021). Roma people may also lack healthcare and access to medicines due to their exclusion from the statutory health insurance system in Romania.

Certain parts of the population are also excluded from statutory health systems in countries that consider themselves to have universal or 'near-to universal' coverage. For example, in Bulgaria in 2016, over a quarter (27.5%) of the population was uninsured and in Estonia in 2017 only 86% of the working-age population was insured for the whole year (Palm et al. 2021).

Key findings

- Several macro-level factors beyond health system organisation, financing and delivery, have been found to impact patient access to medicines: such as economic factors, patients' socio-economic status and ability to pay, health system characteristics, and cultural and political factors.
- There is a positive relationship between country income and availability of medicines.
- Patient socio-economic status as well as insurance status and preferences, can impact physician prescribing behaviour, which can, in turn, influence access.
- 'Health system readiness', the value that a country places on a medicine, and health system priorities have been found to influence availability of medicinal products.
- Social stigma against specific population groups is noted to cause patients in these populations to have partial access to or be excluded from treatment and care due to occasional or perceived discrimination.

Discussion

Using a conceptual framework outlining the key stages of market access pathways for pharmaceuticals both at EU and country level, we have (i) identified the key factors and challenges contributing to patient access delays in Europe, (ii) examined the possible impact these factors might have on patient access throughout the required stages a medicine goes through to become available to patients and (iii) provided recommendations across key areas to improve patient access. Secondary evidence was used to help identify the key factors, which may cause delays to patient access in Europe across the market access pathway (Figure 1) and, where possible, for specific findings for oncology and HIV/AIDS.

Identification of key challenges for patient access in Europe

Overall, a number of concerns have been raised with regards to access to innovative medicines in Europe, particularly in the context of oncology and HIV/AIDS medicines. In this section we identify the main challenges observed for patient access in Europe, across both the market access pathway and specific therapeutic areas. A summary of the challenges for patient access within and across countries is provided on page 80.

Challenges across the market access pathway

Despite efforts to ensure availability of medicines and expedite patient access at EU level, evidence from the literature suggests that access (determined by availability and affordability) to innovative medicines in Europe is still challenging and subject to delays across different therapeutic areas and indications. Availability and affordability are not mutually exclusive but are equally important in ensuring whether patients across countries are able to access needed medicines: setting affordable prices or establishing availability within a country does not necessarily equate to access. Availability and affordability are closely intertwined, with the latter determining the former and vice versa: availability of medicines is often dictated by the ability of healthcare systems (and, where coverage is incomplete, patients) to afford innovative medicines. Affordability is one of the most critical factors contributing to patient and market access and can have profound impact on availability, as failure to conclude reimbursement negotiations and arrive at affordable prices for new medicines can substantially delay or hinder access.

Table 3 provides a visual overview and assessment of the evidence reviewed in this study. As this study reviews the evidence across the complete product pathway in 29 countries, this table intrinsically generalizes and summarizes the findings to a cross-country level. The judgements made in these tables are obtained by an overall assessment of the evidence reviewed in each

section, judging whether the evidence suggests an overwhelmingly negative impact on access, an overwhelmingly positive impact on access, or whether evidence is mixed or suggests a position between these two points. Because of this, it is important to note this table provides a simplified review of the material discussed in previous sections and note that country- or policy-specific contexts and systems will have a final impact on whether these statements hold true in every setting or region. Reference can be made to Sections 5 to 13 of this study for a full explanation of the information that motivates this summary.

The findings summarized in Table 3 show that evidence for a majority of endpoints showcases potential negative impacts which are driven by specific policy design or implementation or inter- or cross-country variation. Therefore, they are not necessarily inherently a negative factor for patient access, but the eventual outcome is driven either by design or by other characteristics. It is important to note this in the context of the following discussion, as the true effect of specific areas within the pathway need to be reviewed with the caveat that this effect, and any subsequent implementation of reforms or amendments, needs to take the design of a policy and/or specific circumstances for a country or region into account.

In this section key challenges for patient access across four issues are discussed: time delays, affordability, availability, and geographic variation.

Table 3: The potential impact on access of key endpoints across the patient access pathway

		Mostly negative impact	Potentially negative impact, dependent on country or policy context	Neutral or no impact	Potentially positive impact, dependent on country or policy context	Mostly positive impact	Notes	
Marketing authorization	Timelines and time delays	[Red bar]					-	
	Policy procedures and implementation	[Red bar]					-	
	Evidentiary requirements	[Red bar]		[Orange bar]			-	
	Additional schemes: early dialogue and parallel scientific advice				[Green bar]		-	
	Additional schemes: compassionate use programmes				[Green bar]		1	
Pricing	Timelines and time delays	[Red bar]					2	
	Policy procedures and implementation	[Red bar]					2	
	Evidentiary requirements	[Red bar]					-	
	Company strategy (launch sequencing etc.)	[Red bar]					-	
	Policy outcomes (cost-containment, price levels)	[Red bar]					2	
Health technology assessment	Timelines and time delays	[Red bar]					-	
	HTA assessment at national, regional and hospital level	[Red bar]					3	
	Conditional HTA recommendations	[Red bar]					-	
	HTA models	[Red bar]					-	
	Stakeholder involvement in HTA assessment				[Yellow bar]		-	
	Policy procedures and implementation	[Red bar]					3	
	Evidentiary requirements	[Red bar]					-	
	HTA recommendations and funding decisions	[Red bar]					-	
Pricing and reimbursement negotiations	HTA resubmission and statutory re-assessment				[Yellow bar]		-	
	Other initiatives: early scientific advice and horizon scanning				[Green bar]		-	
	Timelines and time delays	[Red bar]					-	
	Policy procedures and implementation	[Red bar]					-	
	Evidentiary requirements	[Red bar]					-	
	Commercial access agreements	Timelines and time delays	[Red bar]		[Orange bar]			4
		Policy procedures and implementation	[Red bar]					-
		Evidentiary requirements	[Red bar]					-
Institutional funding mechanisms	Type of arrangements and circumstances				[Yellow bar]		-	
	Policy procedures and implementation	[Red bar]					-	
New funding mechanisms	Outcomes				[Green bar]		-	
	Timelines and time delays				[Yellow bar]		5	
	Policy procedures and implementation	[Red bar]					-	
	Evidentiary requirements				[Yellow bar]		-	
	Impact of purchasing and procurement agreements	[Red bar]					-	

Market uptake and diffusion	Supply chain challenges			-
	Patient uptake			-
Macro-factors	Economic factors			-
	Socio-economic status			6
	Health system issues			-
	Cultural and political issues			-
Notes:	¹ In theory, but evidence is unclear or mixed on the effectiveness of specific programmes.			
	² Evidence varies across different pricing regulations			
	³ Variations in HTA systems, procedures, and implementation can manifest themselves either within or across countries.			
	⁴ In general, commercial access are expected to improve patient access. Lengthy or stalled negotiations can have a detrimental effect on timelines.			
	⁵ RWE is commonly expected to minimize evidence gaps, though specific factors in collection and interpretation may hinder the achievement of such aims.			
	⁶ Evidence suggests socio-economic status may play a role in access and uptake, but this is likely only at a physician level.			

Time delays

Evidence shows the patient access pathway is prone to time delays, given the various stages, numerous stakeholders involved and the complexity of pricing and reimbursement processes at national level.

Regulatory issues. Various schemes are available to accelerate marketing authorization processes and shorten time to patient access at both European and national levels. Some of these efforts, such as compassionate use programs prior to marketing authorization, have proven to be successful in achieving patient access in some countries such as France, Spain, and the UK for medicines which would not have been otherwise available. However, evidence on whether other efforts manage to reduce timelines or improve patient access varies. Efforts at EU level and by national governments seem to, at times, be counterproductive, duplicative, and/or not well orchestrated resulting in time-consuming and lengthy processes and in manufacturer reluctance to apply or pursue new schemes. Effects may also vary at different stages: certain tools, such as CMA, may facilitate access at one stage of the process and delay access in later stages, such as formal assessment by HTA agencies due to the acceptance of low-quality evidence. In addition, clock-stops both at regulatory and HTA level are one of the main factors contributing to access delays.

Pricing. Overall, ERP design and implementation can further contribute to late access, together with requirements for the pricing or reimbursement process to not commence before prices in ERP reference countries are set and a subsequent price calculation occurs. ERP can also lead to potential launch strategies, with a particular impact for noted for Eastern European markets and smaller markets as their position towards the end of launch sequencing strategies may result in longer launch delays. Countries with lower prices or lower market volumes tend to have fewer available medicines and longer delays in medicine launches. Delays associated with other pricing policies are also documented: for example, VBP may not be optimal in delivering faster access due its resource-intensive and frequently time-consuming processes and the considerable time taken for discussions on value between authorities and manufacturers. Mixed pricing methods observed in some European countries such as Germany and France, rely on ERP as a 'safeguard' for price setting through VBP but may see tension may arise between the joint operation of these two methods if the design of suitable methodological and procedural systems is inadequate.

HTA, other funding modalities and MEAs. Time delays are observed at HTA level and depend on: (i) whether a technology undergoes HTA simultaneously to the MA assessment or only post-MA approval; (ii) the time taken for the completion and publication of the HTA process and outcome, and; (iii) the time taken for a positive HTA recommendation to be translated into a funding decision and, further, for the funding decision to be implemented at health system level. MEAs have been introduced to ensure access to new and expensive treatments, but the type of

agreement used and the accompanied negotiation process both play a crucial role in whether time delays to patient access occur. MYMI agreements implemented in Belgium, Denmark and the Netherlands have proven to significantly minimize the time taken for reimbursement approval of medicines with multiple indications.

Affordability

The purchasing ability of countries and patients, and medicine price levels, can determine whether treatments are affordable and, subsequently, available within markets. High medicine prices can have a direct impact on affordability and indirect contribution to time delays. Poor allocation of resources and budget planning at healthcare system level can also result in low affordability due to limited availability of funding for the reimbursement of innovative medicines. In addition, this might have a knock-on effect on the uptake and diffusion of highly innovative medicines at regional and hospital level due to the unavailability of these medicines at national level. To improve availability and reduce delays, the design and implementation of pricing and reimbursement policies should be adapted to balance value and affordability.

There is mixed evidence on how pricing regulations affect the affordability of medicines, notably in terms of their impact on price levels and contributions to cost-containment aims. MEAs can address affordability concerns to a degree by enabling purchasers and manufacturers to negotiate prices of innovative medicines which are associated with high uncertainty around their likely clinical benefit due to immature data and/or early phase evidence. Under the right conditions, MEAs can improve access to innovative technologies, reward research and development, and create a system of pay-for-outcome by aligning investment with return. In addition, from a healthcare system perspective, MEAs can enhance affordability and ensure access to medicines which may not have been available otherwise due to high evidence uncertainty. Similarly, alternative coverage options such as special or earmarked funds, and special purchasing processes can provide access to medicines which are not accessible and reimbursed by the national health system of a country.

While affordability issues can be determined and partly managed by pricing and reimbursement policies, other factors may have a further impact. Evidence showed there is a negative relationship between a country's income and delays in medicine availability. Uptake and diffusion of medicines can also, in part, be dictated by physician prescribing behaviour, which in turn can indirectly be affected by other external factors such as patients' socioeconomic status.

Availability

Availability issues are well documented throughout the different stages and levels of the European market access process, where factors at each stage can affect availability. For instance, despite receiving marketing authorization at EU level, numerous advanced therapies

were not reimbursed at national level due to insufficient comparative effectiveness data deemed necessary during their local value assessment processes. Evidence also showed that countries with strict pricing regulations, such as ERP, may disincentivize manufacturers to make their products available in markets where prices are low and have no provisions to reward innovation, leading to product shortages. Product shortages have been observed in oncology drugs: 45% of respondents in a 2013 survey of the impact of drug shortages in Europe stated life preserving drugs such as oncology drugs were affected by drug shortages (Pauwels et al. 2015). Parallel trade is also shown to result in product shortages in lower-priced markets, contributing to patient access discrepancies across Europe.

During HTA and reimbursement negotiations, variation in the availability of medicines across countries is attributed to different evidentiary requirements, differences in the willingness to pay thresholds across countries, divergence in the interpretation of evidence and different dimensions of value considered during these processes. The possibility of resubmitting evidence for HTA reassessment gives manufacturers the opportunity to alter previously negative recommendations and impacts availability.

While new funding mechanisms such as MEAs and specialized funds contribute to availability of medicines within countries, tendering and procurement might have an ambiguous impact on treatment availability. Even though therapeutic tendering is predominately used for off-patent medicines, generics, and biosimilars, introducing therapeutic tenders for in-patent medicines based on multiple technology assessments at HTA level to identify interchangeable treatments under the same indication could potentially increase affordability and availability of medicines and help ensure timely access to affordable medicines for patients (Wouters et al. 2019). However, therapeutic tendering may lead to product shortages by relying on fewer firms for the supply of medicines (Wouters et al., 2019) and by pushing treatment prices downwards (Vogler et al. 2017). In contrast to therapeutic tendering, tenders for non-interchangeable medicines such as in-patent medicines and biosimilars can be quite challenging due to limited treatment options, potential market shortages and limited prescribing freedom. Overall, differences in legal, regulatory, and policy procedures and implementation may pose additional challenges for the efficient implementation of tendering mechanisms, with immediate implications for availability.

Different initiatives, such as horizon scanning and early dialogue, have been introduced in some countries at both regulatory and HTA level with the aim of contributing to faster and more positive recommendations. By introducing these initiatives, issues such as ambiguity of national requirements, evidence gaps, and misalignment on value and price could be overcome at earlier stages and ultimately help avoid availability issues. Other solutions, such as parallel review processes established in Australia, England and Canada, still need to be developed and

implemented in Europe to expedite patient access to medicines, minimize delays occurring at the first stages of MA and HTA assessment, and ensure immediate availability of medicines at national level.

Inter- and intra-country variations in market and patient access

The most recent W.A.I.T indicator shows varying rates of availability in Europe, measured by the number of total medicines available to patients in 2020. The highest rates in availability were reported in Germany (88% of a total of 152 EMA products available in Germany), Denmark (86%) and Austria (82%) and the lowest rates in Lithuania (17%), Latvia (15%), and Serbia (5%) (IQVIA 2021).

Overall, variations in market and patient access *across countries* can be attributed to several reasons arising throughout the access pathway of a medicine related to the organisation of the healthcare system, national pricing and reimbursement policies, value considerations, health system priorities, and manufacturers' launching strategies. Unequal access and imbalanced availability observed across countries can arise due to spillover effects caused by the nature of pricing and reimbursement policies designed and implemented within countries, and can be caused by divergent HTA recommendations, which are influenced by differences in (a) the design and operation of HTA systems; (b) HTA processes, including administrative provisions; (c) evidentiary requirements and acceptance of specific types of evidence; and (d) explicit or implicit consideration of wider dimensions of benefit beyond costs and effects.

Such variations are furthered by divergent stakeholder objectives: (a) the healthcare system, as the purchaser and commissioner of health care goods and services, striving for efficient allocation of scarce resources and; (b) the supply-side aiming towards maximising return on investment. Other country-specific provisions, such as supply chain arrangements, taxes and tariffs applied on pharmaceuticals, can have a knock-on effect on patient access leading to more cross-country variation impacting affordability, availability, and timely patient access.

Variations in patient access may also occur *within countries*. Some HTA systems are characterized by a devolved structure where assessments and reimbursement decisions take place at different levels: operating HTA at different levels may result in divergent decisions due to differences in both the methodologies used across levels (for example, local budget impact analyses at regional level) and the technologies subject to evaluation across levels, which in turn may lead to experiences of inequalities in access. Divergent cross-country HTA outcomes, translating into diverging access outcomes for the same medicine, were further observed during negotiation processes and, notably, in the endpoints considered, their weight and the way they are incorporated in the final decision.

Countries with decentralized health care systems may experience these variations more intensely: resources and budget constraints at regional or local (hospital) level may limit the incorporation of new technologies into clinical practice. Regional and/or local funding options may have considerable impact on both the timing and the number of new medicines available for patients from region to region. A fragmented pharmaceutical sector within a country may also limit the bargaining power of public procurement bodies considerably and dis-incentivize collaborative procurement strategies among purchasers.

Additional contextual factors may also impact patient access. Income levels and market size could be important determinants of new medicines' launch: in comparison to higher income countries, lower income countries experience poorer access and low new medicine uptake. Beyond the effects of manufacturers' launch sequencing strategies, lower income countries tend to have weaker negotiating and bargaining power during reimbursement negotiations. The preparedness and readiness of health systems to respond to novel interventions and tools further impacts access to new medicines. Access may also be impeded by the effects of institutional path dependency, the thought processes that underly the current practices, existing frameworks and bureaucracy, all of which limit the health system flexibility.

Challenges across therapeutic areas

The focus on the issues of patient access in HIV/AIDS and oncology produced only intermittent evidence on access delays; these related mostly to HIV/AIDS. Table 4 provides an assessment of the evidence across various pathway stages for both therapeutic areas. As seen in Table 4, very limited evidence was found on access delays which exist for oncology or HIV/AIDS medicines. The evidence which was found is summarized here.

Differences in access across countries. The reviewed evidence suggests that variation in access may be due to regional differences in perspectives, treatment and management of a given condition. Inter-country variation in patient access may also be furthered by differences in willingness to pay, the capacity of the healthcare system, and societal priorities. As seen in Table 4, while limited evidence is available for HIV/AIDS, it tends to focus on elements outside the 'access pathway' and highlights the impact of social and cultural effects: social stigma and, in a minority of cases, criminalisation of either HIV/AIDS or activities associated with HIV/AIDS²¹, seem to be strong determinants for diagnosis and subsequent treatment. Macro-economic factors may also influence access to medicines: country income also seems positively associated with the speed of incorporating new products in treatment regimens.

Some therapeutic areas deemed to have high unmet need may benefit from assistance throughout the market access pathway, such as conditional approval, additional time for post-

²¹ For example, drug use or sex work (ECDC 2017).

approval evidence submission, or the acceptance of RWE. In the W.A.I.T indicator, England had a better availability score for oncology products than for all medicines, which could be due to the existence of the CDF (IQVIA 2021). Further evidence on oncology shows that key mechanisms aiding reimbursement, such as commercial access agreements, institutional funding mechanisms and new funding mechanisms are thought to have a positive impact on access, while marketing authorization and HTA can also result in a potentially positive impact. The use and/or acceptance of such tools or support varies across European countries and some of these dedicated tools can have a detrimental effect on timely access; for example, authorization under exceptional circumstances, is thought to have a detrimental effect on time-to-market for both HIV/AIDS and oncology products when compared with standard authorization procedures, in terms of much longer review times (Boon et al., 2010).

Differences in access within countries. Variation in access for specific therapeutic areas (e.g., oncology products) is also seen to exist within countries, particularly in those with a decentralized structure in their health care system (e.g., Italy) and where products are either made available with a delay or not at all in some regions.

Measures for improving disease-specific access. A number of measures have been identified that contribute to access to new medicines, specifically in oncology and HIV/AIDS. New methods for pricing of combination therapies for oncology are only implemented in France and the United Kingdom, but more countries could look to utilizing similar methods to adapt existing practices to reflect the requirements of such products, which can also have implications for patient access.

Evidence uncertainties, particularly in oncology, could be addressed through the use and acceptance of new clinical study designs (e.g., basket trials, umbrella trials, among others), real world data, in addition to more active involvement of stakeholders and the consideration of additional dimensions of value beyond costs and effects.

Evidence has shown that MEAs have contributed significantly to improvements in market access for oncology medicines and enabled access to combination therapies, which are increasingly relevant in oncology and HIV/AIDS.

The availability of other dedicated funds may further contribute to the improvement of access of oncology medicines. The Italian Innovation Fund is one good practice example, which has incentivized access to innovative medicines and enabled faster patient access by removing budgetary restrictions at regional level through two separate funds dedicated to highly innovative oncology and non-oncology drugs, respectively.

Table 4: The potential impact on access of key endpoints across therapeutic areas

		Mostly negative impact	Potentially negative impact, dependent on country or policy context	Neutral or no impact	Potentially positive impact, dependent on country or policy context	Mostly positive impact	Notes
Marketing authorization	HIV/AIDS	Potentially positive impact, dependent on country or policy context					-
	Oncology	Potentially positive impact, dependent on country or policy context					-
Pricing	HIV/AIDS						No evidence
	Oncology						No evidence
Health technology assessment	HIV/AIDS						No evidence
	Oncology	Potentially positive impact, dependent on country or policy context					-
Pricing and reimbursement negotiations	HIV/AIDS						No evidence
	Oncology						No evidence
Commercial access agreements	HIV/AIDS	Potentially positive impact, dependent on country or policy context					1
	Oncology	Mostly positive impact					-
Institutional funding mechanisms	HIV/AIDS						No evidence
	Oncology	Mostly positive impact					-
New funding mechanisms	HIV/AIDS						No evidence
	Oncology	Mostly positive impact					-
Market uptake and diffusion	HIV/AIDS						No evidence
	Oncology	Mostly negative impact					2
Macro-factors	HIV/AIDS	Mostly negative impact					-
	Oncology						No evidence
Notes:	¹ This assessment is based on the potential to fund combination therapies, increasingly used in HIV/AIDS, through commercial access agreements. ² This assessment pertains to the endpoint on patient uptake, which raised issues surrounding slow clinical guidance updates. No evidence was found on the impact of other endpoints for market update and diffusion: supply chain challenges and the impact of purchasing agreements.						

Key challenges for patient access

1. **Lengthy MA approval times** because of clock-stops and/or long timeframe for opinions and decisions to be reached.
2. **Command and control pricing systems**, such as ERP, or **pricing systems with high administrative or evidence requirements**.
3. **Potential for pricing systems (e.g., ERP) to encourage sequenced product launches**, though difficulties in ascertaining the extent to which launches are delayed in certain countries remain.
4. **The timing of HTA processes**, notably the point at which the HTA process commences, the length of the HTA process itself, and the time it takes for a positive HTA recommendation to be translated into a funding decision and for a funding decision to be implemented.
5. **HTA processes which take place at multiple levels**, such as national, regional and/or hospital level and may result in differential or fragmented coverage and access.
6. **Variation in HTA systems and procedures between countries** can result in unequal availability of medicines across countries, with notable factors including acceptance or not of certain types of evidentiary requirements, willingness-to-pay thresholds, differences in evidence interpretation, and a range of contextual factors including additional dimensions of value raised during appraisal.
7. **Involvement of multiple national HTA and reimbursement authorities in negotiations** increases the complexity and associated workload with potential impact on timelines and access.
8. **Variation in negotiation processes between countries** can result in diverging access outcomes for the same medicine in different countries, with notable factors affecting decision outcomes including: the endpoints considered during the negotiation process, the social value considerations taken into account and their level of weight, and the way (e.g., explicit vs. implicit) they are incorporated in the final decision.
9. **The expiry of managed entry agreements** might prove challenging in terms of continuing patient access, while these agreements are otherwise generally considered positive for patient access.
10. **Rigidities in current pricing and reimbursement mechanisms and a lack of capacity and/or established legal or regulatory frameworks** may impede adaptation to new data and uptake of innovative funding models that would otherwise have the potential to facilitate access to treatments.
11. **Geographical factors (location of patients and care provision)**, as rural locations may experience slower adoption of new therapies when compared to urban locations.
12. **Health system and macro level factors**, such as a country's healthcare system, the way the system operates, socioeconomic profiles and the tailoring of policies to country contexts and healthcare priorities, as well as income level and market size can influence patient access. For specific therapeutic areas willingness to pay, the capacity of the healthcare system, and societal priorities may also contribute to patient access.
13. **Physician adherence to clinical guidance** and, specifically, the introduction of new therapies.
14. **Social stigma** around specific disease or against certain groups in society, particularly among health professionals and/or key populations, may impact how those diagnosed with certain conditions are accessing treatments.

Considerations for policy change

In November 2020, the European Commission published a proposal for a new “Pharmaceutical Strategy for Europe” with one of four priority points focusing on access to affordable medicines for patients and addressing unmet medical need (EC 2020). Our study has highlighted continued access challenges across all stages of the market access pathway, despite the introduction of many schemes and initiatives to optimize it. Considerations for policy change and improvements of major issues in patient access have been drawn up for each of the stages in the market access pathway, aiming to provide guidance on short-, medium- and long-term options for change or focal points to overcome challenges to access in Europe and in the context of the upcoming Pharmaceutical Strategy.

We provide an agenda for policy change in this section which will not apply fully across all countries in Europe. Equally, any intervention may not operate individually or as a standalone solution as the various aspects of the access pathway are closely interlinked and often influenced by each other.

Regulation

1. **Focus on horizon scanning and early dialogue to maximize the ability and impact of authorization pathways designed for early patient access.** Horizon scanning can be a catalyst for health care systems to better prepare for the introduction of new therapies. Early dialogue or early scientific advice is vital to ensure a common understanding and agreement on scientific requirements for regulatory approval. This should be used extensively with the widest possible participation of the broader stakeholder community, including a representation by HTA bodies and the patient community. The IHSI (previously the BeNeLuxA horizon scanning initiative) serves as a good practice case at European level.
2. **Strengthen cooperation between regulatory agencies and national HTA agencies through the establishment of parallel review processes.** These processes can help mitigate access tensions across countries occurring due to differences in evidence requirements and ensure market availability across all stages. Although some countries have established such processes for certain products (e.g., oncology medicines in the UK) and compassionate use programmes exist in general offering access pathways (e.g., ATU in France and EAMS in the UK, among others), these remain partial options. Countries could also seek to start pricing and reimbursement processes after a positive CHMP decision but prior to EMA approval, such as seen in Denmark, Italy, and Portugal.

Pricing

3. **Review whether pricing and reimbursement systems allow the greatest value to be derived from novel treatments.** Health systems should assess opportunities to adjust prices to local ability to pay to reduce access concerns based on affordability.
4. **Pricing policies promoting evidence-based price-setting should be implemented in the context of highly specialized therapies, instead of command-and-control policies, such as ERP.** Timely patient access can be achieved for these technologies targeting unmet needs by avoiding launch delays and eliminating sequencing.
5. **Improve the design and implementation of pricing systems and move towards pricing policies that are less administratively complex and consider the therapeutic value new medicines.** This is particularly notable for countries which implement ERP systems, for which key features of the design and administration of the system have been linked to delays in patient access.
6. **Where necessary, modify certain elements of ERP systems, such as the frequency of price revisions, the basket size, and reliance on reference countries with intense price regulations, to avoid spillover effects from ERP.**

Health technology assessment

7. **Monitor the time taken for the completion of HTAs and funding decisions.** Currently, the speed with which HTAs are conducted varies across countries, creating a significant impact on patient access. Two major contributors to delays are (i) reviews of evidence submitted for HTA applications, and (ii) negotiation timelines. Practical solutions to these could be offering early dialogue, rapid review or fast-track assessments and limiting or capping negotiation timelines after HTA recommendations.
8. **Create special assessment pathways or tailor-made criteria for the evaluation of highly specialized treatments usually associated with high degree of uncertainty due to limited evidence.** Action to this end will have to be system-specific, but examples of potential directions include (a) utilizing designated assessment pathways or processes, (b) considering MEAs during economic evaluation, and (c) involving stakeholders throughout to ensure that relevant endpoints and dimensions of benefit are taken into consideration. Such changes would allow HTA processes to be more reflective of healthcare needs and scientific developments while impacting patient access positively.
9. **Improve coordination of HTA processes in countries with decentralized systems.** One way this could be achieved is through the conduct of clinical benefit assessments at national level, and economic evaluations at regional and/or provider level to allow for reflection of local needs and budgets. Regardless, local budgets and financial resources may continue to influence availability or acceptance of the same medicine across regions.

10. **Invest in the infrastructure and development of joint mechanisms for RWE generation and EU-wide registries to address evidentiary gaps.** Where significant uncertainty occurs during the assessment and appraisal process, collecting RWE through registries or other forms of evidence generation (e.g., observational studies) using validated designs can mitigate limited evidence. Efforts should align with high quality standards agreed amongst key stakeholders, (regulatory agencies and governments), to effectively deal with 'big data' resulting from registries and further utilize these data to improve reimbursement decisions.
11. **Leverage current cooperation across European countries for health technology assessments,** specifically for joint clinical assessment across EU member states and the proposed EU regulation on HTA cooperation. Other efforts include the Finland, Norway, and Sweden HTA collaboration network (FINOSE), which brings together Sweden's TLV, the Norwegian Medicines Agency (NOMA) and the Finnish Medicines Agency (FIMA) to pilot cooperation on efficacy assessments with the aim of improving patient access (Eatwell & Swierczyna, 2019; Norwegian Medicines Agency et al., 2018).

Reimbursement

12. **Rely on RWE during reimbursement negotiations,** especially considering incomplete evidence across EU countries, to ensure evidence required under MEAs is provided in a timely manner.
13. **Establish therapeutic area-specific solutions for data generation, budgeting/funding, or other bottlenecks.** Some countries in Europe are already implementing area-specific solutions to improve patient access, such as DRUP in the Netherlands which creates an alternative data generation pathway for precision oncology medicines for small populations. Such solutions may need to be accompanied by decisions to prioritize medicines with higher clinical value, where budgets are limited. The impact of such efforts needs to be assessed.
14. **Use MEAs or other novel funding mechanisms to optimize reimbursement, particularly in areas of significant unmet medical need.** However, this must be accompanied by built-in adaptation for termination where updated data supports the discontinuation of funding of a medicine under an MEA (Vogler et al., 2018), to ensure available financial resources are used efficiently and effectively.

Market uptake and diffusion

15. **Ensure clinical guidelines and/or care pathways are as up to date as possible,** allowing physicians to prescribe the most recently approved medicines. This can be

achieved through reviews of clinical guidelines upon introduction of new, clinically- and cost- effective treatments to the market.

- 16. Collect evidence on country-specific factors inhibiting the diffusion of medicines** to add to current evidence and contribute to market forecasting. Evidence can be generated through established performance metrics to quantify behaviour which impact diffusion and uptake such as physician prescribing, pharmacist dispensing, and patient awareness and knowledge.

Macro-level factors and wider system needs

- 17. Ensure accurate and timely diagnosis and treatment initiation through accessible screening and diagnosis programmes.** Countries should review their current preventative and early diagnostic tools for key disease areas, with a view to updating these where they are lacking for which they can look to other countries/regions for best practices.
- 18. For HIV specifically, have measures in place at national/community level.** Such measures relate to the reduction in a) the criminalisation of HIV and/or related activities where possible and b) social stigma against HIV/AIDS. The degree to which countries have implemented widespread screening or targeted diagnosis of at-risk patients varies significantly across the EU and are worsened by certain settings, which discourage those at risk or with a diagnosis to seek treatment.
- 19. Minimize intra-country variations, which may result in inequitable access and population-level disparities (postcode lottery).** Solutions will have to be tailored to specific countries, but may cover issues of communication, implementation and monitoring, reduction of work duplication, and redefining the scope of specific institutions, among others.
- 20. Conduct and sponsor more research into determinants and challenges for access for specific disease areas to support the refinement of existing tools and the use of novel solutions where possible.** In particular, such research should also consider how the current pathway serves under-represented groups or disease areas, such as HIV/AIDS. Currently, evidence on impact factors for HIV/AIDS across the access pathway are extremely limited, reducing the ability for governments to make informed and evidence-based decisions ensuring access to diagnosis and treatment and reducing rates of infection. Specific country action will depend on existing levels of data collection and analysis in their healthcare system, but at a minimum should seek to collect data for appropriate endpoints in a frequent and regular manner.

21. **Political will is essential to ensure regulatory pathways and value assessment encourage new medicines to come to market.** This will need to be balanced with industry price setting and affordability aims. Additionally, any major institutional change or re-orientation across any part of the access pathway will require recognition of the constraints borne by established structures and is an essential first step to creating a system which is flexible and adaptable.
22. **Strike the right balance between health policy and industrial policy.** The aim of a health system to provide high quality, affordable and timely care to patients is of utmost importance; explicitly considering industrial policy goals, e.g., supporting or incentivising R&D activities, particularly in areas of unmet need, employment, and value added to the economy, could also be part of the overall policy framework. Efforts to this end are long-term and system-wide, but an initial understanding of this balance and where a country wishes to position itself are key to setting a balance which works for that country.
23. **Healthcare systems are constantly and dynamically evolving and need to be able to continuously adapt to changing circumstances,** be flexible to incorporate change, and look forward to upcoming pressures and needs in the short- and long-term.

Conclusion

Patient access to medicines remains a challenge for many, if not most, countries in Europe. This study has set out a conceptual framework covering key features and steps across the patient access pathway to detect key challenges for access. Secondary evidence was identified for all the stages of the framework to showcase where the main access challenges lie. The evidence on access to medicines challenges is well documented across European countries, and is centered around availability, affordability, time impact and geographical variations.

Time delays occur given the complexity of the access pathway and the multiplicity of stakeholders involved. The widespread use of ERP in Europe has several knock-on effects, including launch strategizing and parallel trade, which can have an impact on both availability and affordability. Novel reimbursement mechanisms show the potential for improved access, though limited funding for or uptake of such solutions can result in restricted reimbursement (and, thus, availability) of new medicines.

The unequal access to treatments observed across countries may be because of different policies (e.g., ERP or HTA), the design and operation of a given healthcare system (e.g., the level of decentralization, infrastructure, or the frequency with which clinical guidelines are updated), socioeconomic factors (e.g., income level and market size), and cultural factors (e.g., stigma and discrimination). Variation in access across specific diseases may be due to regional differences in the social perspectives on, and the treatment and management of, a given condition. Our study highlights how factors external to the access pathway can have a significant impact on delaying access; culture and stigma may impact time to and availability of treatments in HIV/AIDS, although there is a dearth of evidence on access challenges and the direct impact of the various market access stages in key disease areas such as HIV/AIDS.

To overcome tensions in the market access pathway and improve patient access to medicines essential for better health outcomes, more strategic efforts should be designed to optimize processes, notably MA, HTA and reimbursement negotiation. The availability of schemes such as early dialogue, early scientific advice and parallel review should be promoted and offered at no additional cost to manufacturers. Harmonisation of evidentiary requirements and common ways to deal with uncertainty may be crucial to reduce discrepancies across countries and avoid duplication of effort. Novel funding mechanisms should be used, where possible, to ameliorate the availability and affordability of medicines. This implies more and better collaboration across countries. Our study has also highlighted the need for an improved evidence base on specific aspects of the pathway (e.g., factors inhibiting the diffusion of medicines, or the use of therapeutic area-specific solutions) and for disease areas (such as HIV/AIDS) to allow for

monitoring of current systems, informed policymaking, and support both amendments to existing tools and the use of novel and groundbreaking solutions.

In order to reduce the challenges and tensions in the pathway and improve the affordability and availability of medicines across and within countries, decision-makers, governments and purchasers of medicines should ensure that regulatory, pricing and reimbursement processes can adapt to the fast-paced and highly innovative health environment and ensure better health outcomes for patients across countries.

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Appendix 1

Appendix Table 1: Conditional market authorization, obligations on manufacturers

Some of the obligations listed by the EMA are as follows:

- full prescribing information and package leaflet with detailed instructions for safe use and conditions for storage
- a robust risk-management and safety monitoring plan
- manufacturing controls including official batch controls for vaccines, as required
- legally binding post-approval obligations (i.e., conditions) for the marketing authorisation holder and a clear legal framework for the evaluation of emerging efficacy and safety data
- a paediatric investigation plan

Source: (EMA 2017b)

Appendix 2

The research question was drafted abiding by the PICO's criteria for formulating a researchable question (Aslam and Emmanuel 2010). Information was collected against the study endpoints through scanning of peer-reviewed and grey literature to investigate available evidence on factors influencing patient access. Search engines such as MEDLINE, PubMed, and Google Scholar, which are commonly used in the fields of health policy and health economics, were used. The search was limited to English language to ensure our full understanding and unbiased interpretation of the available evidence. The search was first limited to publication dates from January 2015 to March 2021 to capture the most recent data and developments of policies as possible and avoid the collection of outdated evidence. However, evidence from earlier years were included for endpoints and stages where information was limited and in cases where it was relevant to our research. As the country scope of the study was quite extensive including all the European member states, Serbia and the UK, the initial search was not limited using the name of the countries in the search terms. However, in the first stage of screening of the resulted papers looking into the title and the abstract for relevance, we included only studies which were focusing on the European context (plus Serbia and the UK). The search strategy is outlined in the table below.

Due to the very extensive evidence resulting from our search strategies, we limited the papers for inclusion to the first fifty papers resulted per each stage following an initial scan of titles. The papers were screened subsequently by their abstract, and the full text of those included based on the initial screening was reviewed for the study endpoints outlined in the analytical framework above and mention of patient access. The number of studies based on evidence at each endpoint was recorded and papers related to multiple stages were referenced in all the relevant sections. Evidence was extracted in excel spreadsheets, one for each stage of a treatment's pathway. The spreadsheets included paper titles in the rows, the relevant endpoints in the columns, while evidence was inserted into the respective cells. A comprehensive synthesis of the literature was carried out to identify key trends related to policies which can impede or ameliorate patient access across Europe.

Table: Search strategy of the scoping literature review

Research Question				
	Population	Intervention	Comparator	Outcomes
PICOs Criteria	Europe, Serbia, and the UK	Policies/interventions/activities in MA, pricing, HTA, reimbursement and other healthcare system wide areas	N/A	Affordability Availability Timely Access
Search engines	MEDLINE, PubMed, Google Scholar, websites of competent authorities including health ministries and regulatory authorities, the WHO, the European Commission (EC), Organisation for the Economic Cooperation and Development (OECD) and the EMA.			
Search Strategies				
Search keywords by stage				
MA	"marketing authorisation"; "standard marketing authorisation"; "standard approval"; "accelerated marketing authorisation"; "accelerated approval"; "conditional marketing authorisation"; "conditional approval"; "exceptional use"; "authorisation under exceptional circumstances"; "exceptional circumstances"; "compassionate use"; "early dialogue"; "early scientific advice"; "parallel review"; "parallel scientific advice"			
Pricing	"pricing regulation(s)"; "pricing policy(ies)"; "pricing"; "external reference pricing"; "external price referencing"; "international benchmarking"; "international referencing"; "international price referencing"; "free pricing"; "value-based pricing"; "cost-effectiveness pricing"; "rate of return pricing"; "pharmaceutical price regulation scheme"; "voluntary scheme"; "price referencing"			
HTA	"health technology assessment"; "HTA"; "value assessment"; "clinical benefit assessment"; "cost-effectiveness assessment"; "value-based assessment"; "evidence-based"; "early dialogue"; "early scientific advice"; "scientific advice"; "horizon scanning"			
Reimbursement	"reimbursement"; "funding"; "coverage"; "negotiation(s)"; "commercial access arrangements"; "commercial access schemes"; "risk sharing"; "managed entry agreements"; "managed entry arrangements"; "institutional funding"; "new funding models"			
Post-market access	"clinical guidance"; "clinical guidelines"; "market diffusion"; "market uptake"; "patient uptake"; "formulary(ies)"; "clawbacks"; "rebates"; "co-payment(s)"; "prescribing"; "prescription"; "adherence"; "procurement"; "budget ceiling"; "capitation payments"; "financial incentives"; "non-financial incentives"; "incentive(s)"; "diagnostic related groups"; "DRG"; "hospital"; "in-patient"; "pharmacy"; "supply chain"; "distribution chain"			
Macro-factors	"financing"; "macro-economic"; "burden of disease"; "socioeconomic"; "GDP"; "health expenditure"; "health spending"; "pharmaceutical expenditure"; "pharmaceutical spending"			
Common search keywords used in all search strategies				
Drug; drugs; medicine; medicines; pharmaceutical; pharmaceuticals				
HIV; AIDS; oncology; cancer				
Europe; Austria; Belgium; Bulgaria; Croatia; Cyprus; Czechia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Netherlands; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Sweden; UK; United Kingdom				
Timelines	1 st January 2015- 31 st August 2021			
Language	English			
Limited to	Title and abstract			