MARKET ACCESS, PRICING AND REIMBURSEMENT PROCESSES FOR ORPHAN DRUGS IN THE EU-5 COUNTRIES: A COMPARATIVE ASSESSMENT

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OBJECTIVE:

- The healthcare system in Europe seems simple at first glance. The European Medicines Agency (EMA) centrally regulates the marketing authorization of new medicines in Europe. However, the health systems are not part of the Lisbon Treaty and therefore in the national accountability of the individual European Union (EU) member states. This means 28 different ways of market access and reimbursement.
- For orphan drugs, the opportunities of market access begin even before the drug approval through EMA. To show the possibilities, the market access, pricing and reimbursement processes of the big five European countries (EU5) - France, Germany, Italy, Spain and the United Kingdom (UK) - were analysed for similarities and differences.

METHODS:

- The national laws and regulations of France, Germany, Italy, Spain and UK were reviewed via targeted literature research, including official health technology assessment (HTA) /reimbursement agency websites. For validation, additional expert interviews were partly conducted:
  - o For France, the Social Security code [1] and the Public Health Code [2], the regulation and guidance of the Haute Autorité de Santé (HAS) [3] and the Economic committee for health products (CEPS) [4] and the general agreement between LEEM (French pharmaceutical industry association) and CEPS [4].
  - o For Germany, the relevant social codebook V [5] and the regulations of the federal joint committee [6] .
  - o For Italy, a current Regulation of the Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA) [7].
  - o For Spain local published targeted literature [8-11], related laws [13] and websites of the competent authorities [9-10,12].
  - o For the UK, regulations and guidance published by the Department of Health and Social Care, National Institute for Health and Care Excellence (NICE), and NHS England [14].

RESULTS:

- In general, there is no extra pathway for orphan drugs in the EU5 with respect to market access, pricing and reimbursement. The main pathways for market access, pricing and reimbursement remain, but with some exceptions that differ country by country. Tables 1 to 5 describe the different situations in each country.

Table 1: Market Access, pricing and reimbursement in France

France	
Authority	High Authority of Health = Haute Autorité de Santé - HAS (benefit assessment & reimbursement status) Economic committee for Health products- Comité économique des produits de santé CEPS (Economic/Pricing)
Timing	No specific timing for OD. For all drugs timing is given by law with 6 months (rarely happens in real life).
Reimbursements starts	… when the reimbursement decision is published in the French Official Journal (JO) as for non-orphan drugs.
Regulations	No specific regulations for Orphan drugs.
Benefits for OD	No specific benefits for Orphan drugs.
Pitfalls	For ultra-rare disease, the reimbursement process can be harder than for non-orphan drugs as the same methodological frame (evidence-based health care) is applied.
Special programs	No special program.
Early Access/ before MA	May enter early access programs if there are no therapeutics alternatives available, whilst under certain circumstances.
What is discussed for the future	No specific reform is discussed for Orphan drugs. However, for all drugs, an HTA reform is in discussion to unify the medical benefit (SMR) and the added medical benefit (ASMR) in one unique criteria called "Relative Therapeutic value" (VTR) with one unique reimbursement rate.

Table 2: Market Access, pricing and reimbursement in Germany

Germany	
Authority	Joint Federal Committee = Gemeinsamer Bundesausschuss G-BA (Benefit Assessment) National Association of Statutory Health Insurance Funds = Spitzenverband der Gesetzlichen Krankenversicherungen - GKV-SV (Price negotiation)
Timing	At the time of marketing authorization, MAH can submit the reimbursement dossier. Free pricing after dossier submission for the first 12 months.
Reimbursements starts	Free pricing for the first 12 months (reimbursement guaranteed in the outpatient setting). After the P&R agreement the new price is applied and reimbursed from the 1st day after month 12.
Regulations	§35a of the Social Code Book V
Benefits for OD	Orphan drugs have an automatic proof for an added benefit by law. There is at least a non-quantifiable added benefit. No data in comparison to an appropriate clinical comparator have to be presented.
Pitfalls	Drugs exceeding the threshold of €50 million revenue within 12 months, are treated as normal drugs, with the consequence of the G-BA requesting a re-submission of a full dossier. G-BA determine the time when the resolution would expire and a re-submission would be required. G-BA could request a post-marketing study to gather data on specific) German-relevant) issue (linked to a determination time).
Special programs	There are no special programs.
Early Access/ before MA	Only normal early access programs do apply.
What is discussed for the future	The rule of an automatic added benefit is questioned by politics and payors, due to manufacturers presenting no sufficient data.

Table 3: Market Access, pricing and reimbursement in Italy

Italy	
Authority	The Italian Medicines Agency = Agenzia Italiana del Farmaco (AIFA)
Timing	After the release of a CHMP positive opinion. There is no difference between the P&R assessment processes of ODs and non-ODs, although theoretically ODs may be subject to the accelerated assessment process of 100 days.
Reimbursements starts	… after the publication of the resolution with the outcomes of the P&R negotiations in the Italian Official Journal (GURI). Access to and reimbursement of ODs are possible before its marketing authorization (i.e. early access programmes: Law 648/96; Law 326/03 - Fondo AIFA 5%) Submission of the Pricing and Reimbursement Dossier (including a drug's price) to AIFA immediately after the CHMP positive opinion (instead of waiting until the Commission's Decision is publicized officially) and access to the accelerated evaluation process.
Regulations	Law 189/12 (so-called Balduzzi Law) and its subsequent amendment - Decree Law 69/13.
Benefits for OD	Pursuant to the Decree Law 69/13, for ODs manufacturing companies may apply for the accelerated P&R process (i.e. 100 instead of 180 days or so-called "fast track authorization"), even though real world data show that time to reimbursement for these drugs is actually significantly longer.
Pitfalls	No specific pitfalls.
Special programs	Not applicable.
Early Access/ before MA	The Italian NHS grants access to a drug even before its marketing authorization ("early access"=L648/96; Italy's Fondo AIFA 5%).
What is discussed for the future	Innovative negotiating models, in addition to conventional schemes (e.g. risk-sharing, price-volume agreements), are currently under discussion.

Table 4: Market Access, pricing and reimbursement in Spain

Spain	
Authority	• Ministry of Health, Consumption and Social Welfare = Ministerio de Sanidad, Consumo y Bienestar Social (MSCB): Spanish Agency of Medicines and Medical Devices = Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). • Directorate-General for Basic Portfolio of Services of the National Health System and Pharmacy = Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia (DGCBSF). • Inter-ministerial Commission for Medicine Prices = Comisión Interministerial de Precios de Medicamentos Y Productos Sanitarios (CIMP).
Timing	After EU marketing authorization, AEMPS gives local marketing authorisation and assigns a national code. This step takes around 1-2 months after EU marketing authorization. Then, drug licence holders can submit the reimbursement dossier after the MSCB initiates the P&R process.
Reimbursements starts	… after clinical and economic assessments by DGCBSF and CIMP and P&R negotiation. As for clinical evaluation, the results of the Therapeutic Positioning Report = IPT (Informe de Posicionamiento Terapéutico) made by the AEMPS have a key role. Median time from national code to commercialization for orphan drugs between 2002-2017 was 13.4 months (range 2.1- 91.7; mean time 20.1 months [SD 17.0]) [8].
Regulations	No specific regulations for orphan drugs in terms of P&R.
Benefits for OD	No specific benefits for orphan drugs. However mandatory price deduction applied for ODs is lower than the one existing for non-ODs.
Pitfalls	No specific pitfalls for orphan drugs.
Special programs	No special programs.
Early Access/ before MA	Only normal early access programs do apply (mostly compassionate use NPP).
What is discussed for the future	Risk sharing agreement role both at national and regional levels. To revise orphan drug price when there is uncertain related to their clinical effectiveness or a substantial increase in the expected target population.

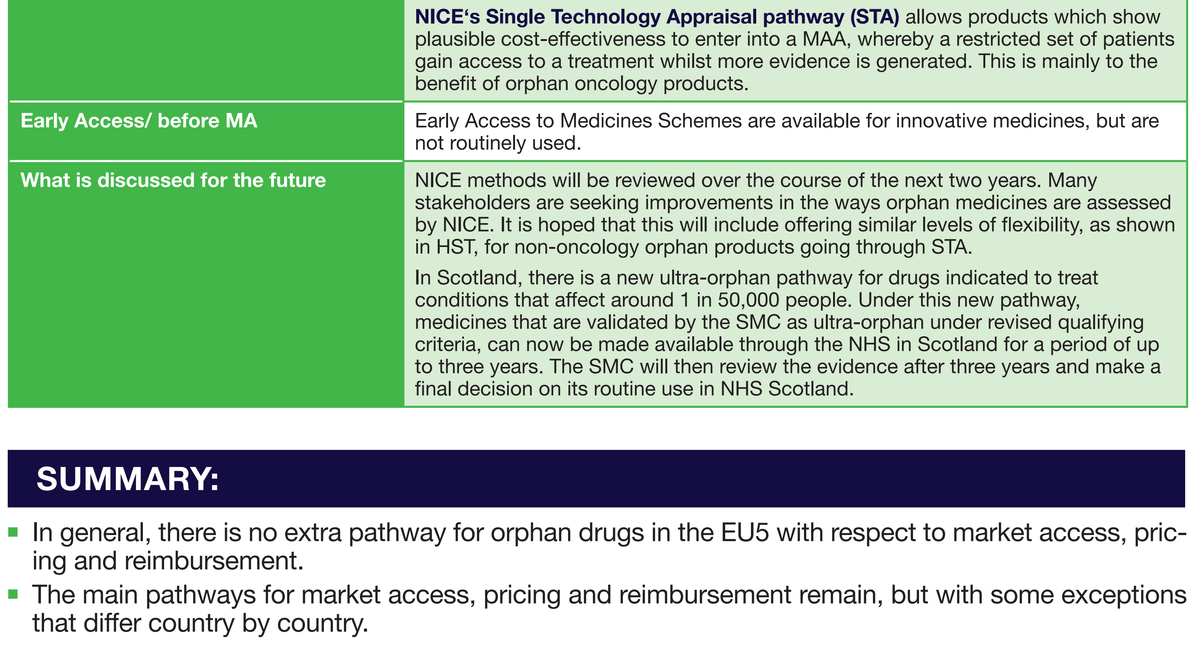
Table 5: Market Access, pricing and reimbursement in UK

United Kingdom	
Authority	National Institute for Health and Care Excellence (NICE)
Timing	After marketing authorization, drug licence holders can submit their dossier. Although, a UK-wide Early Access to Medicines Scheme for life-threatening or seriously debilitating conditions can enable access to some medicines for up to 18 months before formal marketing authorization.
Reimbursements starts	90 days after recommendation for a Single Technology Assessment (STA) and after 30 days for a Highly Specialised Technology (HST).
Regulations	No special regulations.
Benefits for OD	No special benefits.
Pitfalls	HST has a very low bandwidth, only reviewing ~3 products per year. Many orphan medicines are for patient populations that are too small to collect sufficient evidence for STAs and not small enough to qualify for the HST route, and so fall in the middle. The STA Managed Access Agreement (MAA) is only really an option for oncology products through the Cancer Drugs Fund (CDF) .
Special programs	**NICE's Highly Specialised Technology (HST)** appraisal pathway has higher ICER thresholds (up to 300k) which accommodates for orphan products with often poor evidence bases. Positive HST recommendations are typically characterised by MAAs and Patient Access Schemes. **NICE's Single Technology Appraisal pathway (STA)** allows products which show plausible cost-effectiveness to enter into a MAA, whereby a restricted set of patients gain access to a treatment whilst more evidence is generated. This is mainly to the benefit of orphan oncology products.
Early Access/ before MA	Early Access to Medicines Schemes are available for innovative medicines, but are not routinely used.
What is discussed for the future	NICE methods will be reviewed over the course of the next two years. Many stakeholders are seeking improvements in the ways orphan medicines are assessed by NICE. It is hoped that this will include offering similar levels of flexibility, as shown in HST, for non-oncology orphan products going through STA. In Scotland, there is a new ultra-orphan pathway for drugs indicated to treat conditions that affect around 1 in 50,000 people. Under this new pathway, medicines that are validated by the SMC as ultra-orphan under revised qualifying criteria, can now be made available through the NHS in Scotland for a period of up to three years. The SMC will then review the evidence after three years and make a final decision on its routine use in NHS Scotland.

SUMMARY:

- In general, there is no extra pathway for orphan drugs in the EU5 with respect to market access, pricing and reimbursement.
- The main pathways for market access, pricing and reimbursement remain, but with some exceptions that differ country by country.
- An improved pathway through the European reimbursement market can be developed by knowing the specialities and the pitfalls which leads in the end to improved price negotiations.
- Figure 1 shows the summarized pathways for Orphan Drugs in EU5.

Figure 1: Summarized pathways for Orphan Drugs in EU5



REFERENCES:

[1] Legifrance. Code de la Sécurité Sociale, consolidated version October, 14th 2019; https://www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006073189, [last accessed 28 October 2019].
[2] Legifrance. Code de la Santé Publique, consolidated version October, 11th 2019; https://www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665, [last accessed 28 October 2019].
[3] Haute Autorité de Santé – HAS, https://www.has-sante.fr/, [last accessed 28 October 2019].
[4] Comité économique des produits de santé – CEPS, https://solidarites-sante.gouv.fr/ministere/acteurs/instances-rattachees/article/ceps-comite-economique-des-produits-de-sante, [last accessed 28 October 2019].
[5] German Social Code Book V, http://www.gesetze-im-internet.de/sgb_5/SGB_5.pdf, [last accessed 28 October 2019].
[6] German Federal Joint Committee, http://www.g-ba.de, [last accessed 28 October 2019].
[7] Agenzia Italiana del Farmaco (AIFA), https://www.aifa.gov.it/, [last accessed 28 October 2019].
[8] Mestre-Ferrándiz J, Iniesta M, Trapero-Bertran M, Espín J, Brosa M. Analysis of the evolution in the access to orphan medicines in Spain. Gac Sanit. 2019 Apr 20. pii: S0213-9111(19)30081-0. doi: 10.1016/j.gaceta.2019.02.008. [Epub ahead of print], [last accessed 28 October 2019].
[9] Agencia Española de Medicamentos y Productos Sanitarios. https://www.aemps.gob.es/?lang=ca, [last accessed 28 October 2019].
[10] Informes de Posicionamiento Terapéutico. https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm
[11] López N, Pomares E, Cuesta M. Analysis of Spanish therapeutic positioning reports published until 2017. Value health. 2018; 21 (S3): S154.
[12] Ministerio de Sanidad, Consumo y Bienestar Social. Available at: https://www.mscbs.gob.es/, [last accessed 28 October 2019].
[13] Royal Legislative Decree 1/2015, of 24 July, approving the revised text of the Law on Guarantees and Rational Use of Medicines and Health Products were reviewed, https://www.boe.es/boe/dias/2015/07/25/pdfs/BOE-A-2015-8343.pdf, [last accessed 28 October 2019].
[14] National Institute for Health and Care Excellence (NICE), https://www.nice.org.uk, [last accessed 28 October 2019].

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