TIME TO REIMBURSEMENT FOR ORPHAN DRUGS IN EU5 IN THE LAST FIVE YEARS

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INTRODUCTION:

Orphan Drugs (ODs) are developed to treat patients suffering from very serious rare diseases for which no treatment, or at least a satisfactory one, has so far been available. Therefore, fast and comprehensive access to them is extremely important for patients who live with such conditions.

While European Medicines Agency (EMA) accelerates ODs' approval process, Pricing and Reimbursement (P&R) decisions and overall assessment timelines for ODs in each of the EU5 countries do not necessarily reflect this concept, but are often driven by the outcomes of the Health Technology Assessment (HTA) and strongly influenced by the external reference pricing.

In France, ODs do not receive any particular benefits in the evaluation process by the French National Authority for Health (HAS), except if they do not demonstrate a high clinical benefit that might give them a priority for the onset of the assessment process. In Germany, the Federal Joint Committee (G-BA) decides on the probability and extent of the added benefit of new active substances coming to the market. For ODs the added benefit is proven by law, however the G-BA is rating the extent of the added benefit and, according to recent modifications, also the probability of the submitted evidence. In Italy reimbursement conditions of ODs are set through the negotiation between the Italian Medicines Agency (AIFA) and manufacturers. ODs may benefit from a fast track assessment process, aimed to reduce time to access for patients, and from earlier submission of the P&R dossier (i.e. after a positive opinion of the Committee for Medicinal Products for Human Use). In Spain, P&R decisions for ODs are made by the Ministry of Health. P&R process for ODs is the same as for any other new drug and evaluation criteria include disease severity, unmet needs, therapeutic and social benefit, budget impact, therapeutic alternatives and the degree of innovation. In the United Kingdom, ODs, generally undergo the standard Single Technology Assessment procedure as none-ODs. However, for very rare, chronic conditions the highly specialized technology assessment may be applied. Typically, companies are free to launch new chemical entities at a price of their choice, however in order to be able to demonstrate cost-effectiveness, Patient Access Schemes, incorporating confidential simple discounts or managed entry agreements are often applied.

These differences in methodologies might affect time to patient access, potentially creating significant disparities in the availability of new ODs across European countries.

OBJECTIVE:

The primary objective of this analysis was to compare the time to reimbursement (TTR) for ODs in five European countries: France, Germany, Italy, Spain and the United Kingdom (UK).

METHODS:

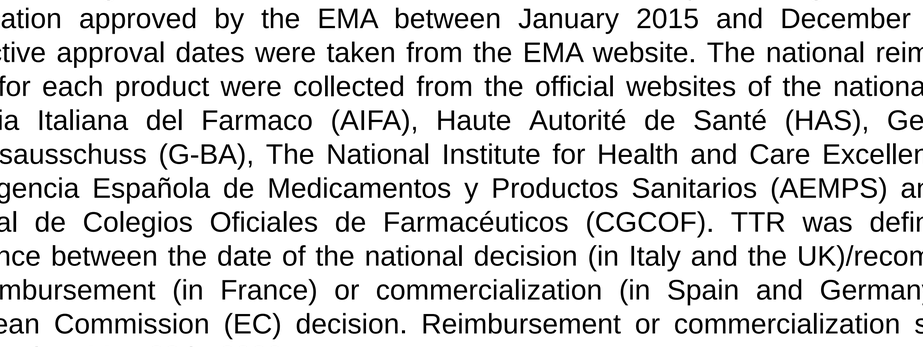
A panel of drugs with new active substances was created by selecting those with orphan designation approved by the EMA between January 2015 and December 2019. The respective approval dates were taken from the EMA website. The national reimbursement dates for each product were collected from the official websites of the national agencies: Agenzia Italiana del Farmaco (AIFA), Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA), The National Institute for Health and Care Excellence (NICE), and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF). TTR was defined as the difference between the date of the national decision (in Italy and the UK)/recommendation for reimbursement (in France) or commercialization (in Spain and Germany) and the European Commission (EC) decision. Reimbursement or commercialization status were evaluated on May 28th, 2020.

RESULTS:

In the considered time-frame (January 2015 to December 2019), 54 ODs received EMA's approval (Table 1). Out of these 54 drugs, 3 (Unituxin®, Zalmoxis® and Lartruvo®) were withdrawn from the market. While Unituxin® had not undergone through the HTA in any of the five countries, Zalmoxis® and Lartruvo® completed the P&R process in the majority of them and, unlike the first, were considered for this analysis. Therefore, our final findings were based on the results of a panel of 53 drugs. The overall percentage of reimbursed drugs ranged from 51% in Spain to 98% in Germany (68% in the UK, 72% in Italy and 91% in France).

Median TTR timelines varied considerably across countries, ranging in Germany from immediate reimbursement available after launch, "real time launch" 37 days (mean 99) to 552 days (mean 559) in Spain, passing through 227 days (mean 281) in France, 350 days (mean 463) in the UK and 417 days (mean 458) in Italy (Figure 1). An overall decrease of median TTR between 2015 and 2018 was from 705 (mean 722) to 321 days (mean 320) in the UK and from 553 (mean 550) to 483 days (mean 455) in Spain. No particular trends with regard to this evaluation were demonstrated in the other three countries.

Figure 1: Median TTR for ODs approved by the EMA between Jan 2015 and Dec 2019 (in days)



EMA: European Medicines Agency; ODs: Orphan drugs; TTR: Time to reimbursement.

Even within every single country ranges between min and max TTR were highly heterogeneous: 72-902 days for France; 67-1078 days for Italy; 132-1390 days for Spain; 135 - 1168 days for the UK. Although drug's launch in Germany is possible immediately after the EC decision, ODs were commercialized within a timeframe of 7-826 days.
Cross-country differences in the number of reimbursed ODs that were approved by the EMA in 2018 and 2019 are particularly interesting (Figure 2).

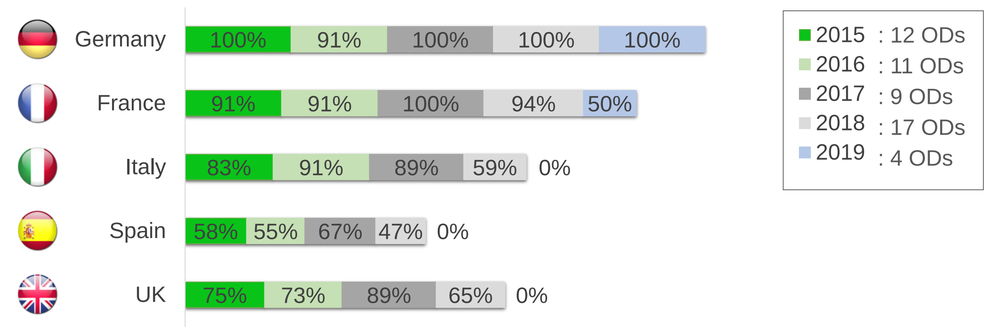
Table 1: List of ODs approved by the EMA between Jan 2015 and Dec 2019

Drug name	Active substance	EC decision	Indication
Cerdelga	eliglustat	19/01/2015	Gaucher Disease
Ofev	nintedanib	14/01/2015	Idiopathic pulmonary fibrosis
Holoclar	autologous human stem cells	17/02/2015	Corneal diseases
Lenvima	lenvatinib	28/05/2015	Thyroid neoplasms
Hetlioz	tasimelteon	03/07/2015	Sleep disorders
Unituxin	dinutuximab	14/08/2015	Neuroblastoma
Farydak	panobinostat	28/08/2015	Multiple myeloma
Kanuma	recombinant human lysosomal acid lipase	28/08/2015	Lysosomal acid lipase deficiency
Strensiq	asfotase alfa	28/08/2015	Hypophosphatasia
Cresemba	isavuconazonium sulfate	15/10/2015	Mucormycosis, invasive aspergillosis
Blincyto	blinatumomab	23/11/2015	Precursor cell lymphoblastic leukemia-lymphoma
Kyprolis	carfilzomib	19/11/2015	Multiple myeloma
Ravicti	glycerol phenylbutyrate	26/11/2015	Urea cycle disorders
Wakix	pitolisant	31/03/2016	Narcolepsy
Alprolix	eftrenonacog alfa	12/05/2016	Haemophilia B
Idelvion	albutrepenonacog alfa	11/05/2016	Hemophilia B
Darzalex	daratumumab	20/05/2016	Multiple myeloma
Galafold	migalastat	25/05/2016	Fabry disease
Strimvelis	autologous CD34+ cell	26/05/2016	Severe combinated immunodeficiency
Zalmoxis	herpes simplex 1 virus-thymidine kinase	18/08/2016	Adjunctive treatment in haematopoietic cell transplantation
Lartruvo	olaratumab	09/11/2016	Sarcoma
Ninlaro	ixazomib	21/11/2016	Multiple myeloma
Ocaliva	obeticholic acid	12/12/2016	Primary biliary cirrhosis
Venclyxto	venetoclax	04/12/2016	Leukemia lymphocytic chronic B-cell
Besponsa	inotuzumab ozogamicin	28/06/2017	Precursor cell lymphoblastic leukemia-lymphoma
Brineura	cerliponase alfa	30/05/2017	Neuronal ceroid-lipofuscinoses
Spinraza	nusinersen sodium	30/05/2017	Muscular atrophy spinal
Oxervate	cenegermin	06/07/2017	Keratitis
Bavencio	avelumab	18/09/2017	Neuroendocrine tumors
Lutathera	lutetium (177Lu) oxodotreotide	26/09/2017	Neuroendocrine tumors
Rydapt	midostaurin	18/09/2017	Leukemia myeloid acute
Xermelo	telotristat	17/09/2017	Carcinoid tumor, neuroendocrine tumors
Zejula	niraparib	16/11/2017	Fallopian tube neoplasms, peritoneal neoplasms, ovarian, neoplasms
Prevymis	letermovir	08/01/2018	Cytomegalovirus infections
Crysvita	burosumab	19/02/2018	Hypophosphatemia
Alofisel	darvadstrocel	23/03/2018	Rectal fistula
Lamzede	velmanase alfa	23/03/2018	Alpha-mannosidosis
Mylotarg	gemtuzumab ozogamicin	19/04/2018	AML
Rubraca	rucaparib	23/05/2018	Ovaric neoplasms
Myalepta	metreleptin	29/07/2018	Lipodystrophy, Familial Partial
Tegsedi	inotersen	05/07/2018	Amyloidosis
Cablivi	caplacizumab	30/08/2018	Purpura, Thrombotic Thrombocytopenic
Kymriah	tisagenlecleucel	22/08/2018	CB-CC, DLBCL
Mepsevii	vestronidase alfa	23/08/2018	Mucopolisaccaridosis VII
Yescarta	axicabtagene ciloleucel	23/08/2018	Lymphoma follicular, Lymphoma large B-cell
Onpattro	patisiran	27/08/2018	Amyloidosis, Familial
Symkevi	tezacaftor / ivacaftor	31/10/2018	Cystic Fibrosis
Poteligeo	mogamulizumab	22/11/2018	Sezary syndrome, mycosis fungoides
Luxturna	voretigene neparvovec	22/11/2018	Retinitis Pigmentosa
Takhzyro	lanadelumab	22/11/2018	Angioedemas, Hereditary
Palynziq	pegvaliase	03/05/2019	Phenylketonurias
Waylivra	volanesorsen	03/05/2019	Hyperlipoproteinemia type I
Zynteglo	autologous CD34+ cell encoding betaA-T87Q-globin gene	29/05/2019	Beta-thalassemia
Xospata	gilteritinib	24/10/2019	Leukemia myeloid acute

ODs: Orphan drugs; EMA: European Medicines Agency.

Our analysis showed that only 47% (8 out of 17), 59% (10 out of 17), and 65% (11 out of 17) of drugs approved by the EMA in 2018 were reimbursed in Spain, Italy, and the UK, respectively, compared to 94% (16 out of 17) of drugs with a positive recommendation for reimbursement in France and 100% of drugs reimbursed in Germany. Besides, the 4 ODs approved by the EMA in 2019 were still not reimbursed in Spain, Italy and the UK at the moment of the analysis, while 50% and 100% were deemed as reimbursed in France and Germany, respectively.

Figure 2: Reimbursed ODs in the EU5 by year of the EC decision (in %)



EC: European Commission; ODs: Orphan drugs.

CONCLUSIONS:

Our analysis demonstrates a wide difference in TTR timelines and number of reimbursed ODs across the EU5, which is likely related to a great heterogeneity of assessment procedures applied by healthcare authorities in these countries.
Current data show that patients in Germany, where reimbursement is automatically granted to each drug from the moment of its dossier submission within the AMNOG process, patients have fastest access to ODs. Among the rest of the countries, France demonstrates the most rapid assessment process for ODs, followed by the UK, Italy, and Spain with a median TTR of 7.5 months, 11.5 months, 13.7 months, and 18.1 months, respectively. It is, however, worth mentioning that in certain cases, longer TTR was likely driven by a delay between the drug's approval by the EMA and the manufacturer's decision to submit a P&R dossier for it, which depended on companies and not local authorities. From 51% to 91% of ODs approved by the EMA between 2015 and 2019 were reimbursed in the four European countries (France, Italy, Spain and the UK) and 98% in Germany. It is likely that these numbers suggest a certain level of disparity in the access to ODs across the EU5.

Our analysis does not consider the additional time required for regional or local negotiations in Italy and Spain, pricing negotiation timing in France, outcomes of the AMNOG assessment process in Germany or incorporation into national commissioning or local funding decisions in the UK. It is based only on publicly available information and the availability of ODs has been documented using different criteria across countries.
Further research is needed to determine the impact of participation in early access programs and drugs' prices on TTR for ODs in the EU5. Further analyses are necessary to properly translate these outcomes into the actual availability of these drugs to patients in Europe.

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