

Time to reimbursement for orphan drugs in EU5 in the last 3 years

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Introduction

Although the orphan drug designation and marketing authorization (MA) are managed and granted at the European level by the European Medicines Agency (EMA), the pricing and reimbursement process is defined on a national level, is often driven by HTA outcomes and is strongly influenced by the external price referencing. In **France** in the SMR evaluation phase there is more flexibility regarding the strength of supporting evidences in orphan drugs (ODs). In **Germany**, the Gemeinsamer Bundesausschuss (GBA) determines only the extent of additional benefit (minor, considerable, major or non-quantifiable), while the categories “no additional benefit” or “less benefit” are not applicable to ODs. Reimbursement goes through the standard process (price freely set by the company and full reimbursement for the first year following the European MA and a negotiation after). In **Italy** prices of ODs and reimbursement by the National Health Service is set through negotiation between the Agenzia Italiana del Farmaco (Italian Medicines Agency-AIFA) and the pharmaceutical companies; ODs can benefit from a fast track assessment process, aimed to reduce time to patient. In **Spain** the central government is in charge of the pricing and reimbursement process of pharmaceutical pricing and reimbursement, while decisions related to the content of the national catalogue of services are responsibility of the Interterritorial Council and decisions related to regional inclusion to the national catalogue of services and management of the regional health services are responsibility of the regional governments. In the **United Kingdom**, both the HTA evaluation and pricing and reimbursement of ODs undergo the same procedure as no ODs, however a less robust HTA assessment might be conducted. Companies are free to launch new branded products at a price of their choice, whether through tenders, Patient Access Schemes, simple discounts or managed entry agreements; at local level prices are often subject to negotiations and the headline “free” price often differs from what the NHS actually pays. These differences in methodologies might affect time to patient access, potentially creating significant disparities in the availability of new ODs across Europe.

Objective

In 2018 data were presented on national reimbursement decisions in terms of time to market (TTR = days elapsed between the European MA and national reimbursement) in France, Germany, Italy, Spain and in the UK for ODs approved by the EMA between January 2016 and September 2017. The aim of this new analysis is to update our previous analysis and to examine whether major changes occurred.

Methods

A panel of drugs was created by selecting the new molecular entities or new combinations of existing molecules (products where the molecule had been launched previously in another indication were excluded from the analysis) approved by the EMA (European Commission Decision) between Jan 2016 and Dec 2018, assessed as ODs. Dates of national reimbursement for each single product have been collected by checking 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).

Results

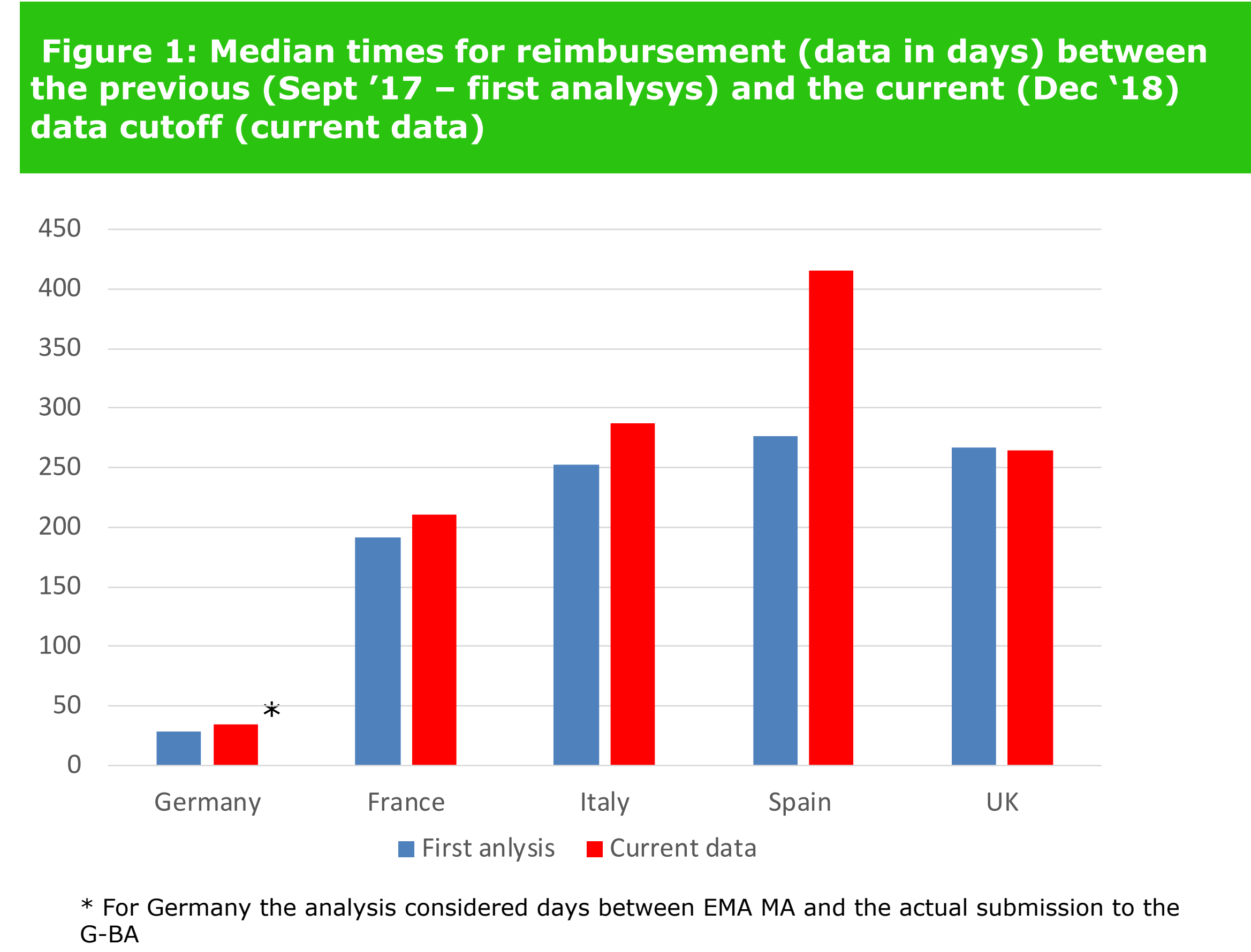
In the considered timeframe, from January 2016 to December 2018, 44 orphan drugs were granted the European approval (European Commission Decision). The overall percentages of reimbursed drugs ranges from 25% in Spain to 100% in Germany (77% in France, 55% in Italy and 45% in the UK). These percentages increased significantly compared to the previous analysis (7% in Spain, 38% in Italy, 45% in France, 28% in the UK and 100% in Germany), due to the longer follow-up and extended data set, longer time frames for the drug assessment, and final registration of the drugs under assessment during the time of the previous analysis.

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Table 1: List of Orphan Drugs approved by EMA between Jan 2016 and Sept 2018 (brand, active substance and indication)				
Brand	Active substance	European MA	Indication	
Alprolix	eftrenonacog alfa	12/05/2016	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).	
Amglidia	glibenclamide	24/05/2018	AMGLIDIA is indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children	
Bavencio	avelumab	18/09/2017	Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).	
Besponsa	inotuzumab ozogamicin	29/06/2017	BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22+ positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).	
Brineura	cerliponase alfa	30/05/2017	Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.	
Cablivi	caplacizumab	31/08/2018	Cablivi is indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.	
Coagadex	human coagulation factor X	16/03/2016	Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.	
Cuprior	trientine	05/09/2017	Cuprior is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.	
Cystadrops	mercaptopamine	19/01/2017	Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis. DARZALEX is indicated: in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy; in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	
Darzalex	daratumumab	20/05/2016	Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation	
Galafold	migalastat cloridrato	26/05/2016	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).	
Idelvion	albutrepenonacog alfa	11/05/2016	Kymriah is indicated for: Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse; Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	
Kymriah	tisagenlecleucel	23/08/2018	Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis	
Lamzede	velmanase alfa	26/09/2017	Lartuvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin	
Lartuvo	olaratumab	09/11/2016	Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients	
Ledaga	mecloretamina	03/03/2017	Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults	
Lutathera	177 Lutetio-dotatato	23/03/2018	Luturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells	
Luxturna	voretigene neparovovec	22/11/2018	Mepsevii is indicated for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome). Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. MYLOTARG is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL)	
Mepsevii	vestronidase alfa	23/08/2018	Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non- dystrophic myotonic disorders.	
Myalepta	metreleptin	30/07/2018	Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone	
MYLOTARG	gemtuzumab ozogamicin	04/05/2018	NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	
Namuscla	mexiletine	18/12/2018	OCALIVA is indicated for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.	
Natpar	parathyroid hormone	24/04/2017	Onpatro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.	
NINLARO	ixazomib citrato	21/11/2016	Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults.	
Ocaliva	acido obetolico	12/12/2016	POTELIGO is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy. Qarziba is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Qarziba should be combined with interleukin-2 (IL-2).	
Onivyde	irinotecan cloridrato	14/10/2016	Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy. Rydapt is indicated: • in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive; • as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).	
Onpatro	patisirian	27/08/2018	Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.	
Oxervate	cenegermin	06/07/2017	Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available	
Poteligeo	mogamolizumab	22/11/2018	Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977, R1070W, D1152H, 2789GG→TA, 2772-28A→G, and 3849T→C.	
Quarziba	dinutuximab beta	08/05/2017	TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.	
Rubraca	rucaparib	24/05/2018	Tag sedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR). Venclxyto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. Venclxyto monotherapy is indicated for the treatment of CLL: • in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.	
Rydapt	midostaurin	18/09/2017	Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.	
Spinraza	nusinersen	30/05/2017	Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	
Strimvelis	autologous CD34+ enriched cells transduced with retroviral vector	26/05/2016	Xermelo is indicated for the treatment of carcinoïd syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.	
Symkevi	tezacaftor / ivacaftor	31/10/2018	Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBLCL), after two or more lines of systemic therapy	
Takhzyro	lanadelumab	22/11/2018	Zalmoxis is indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies	
Tegsedi	inotersen	06/07/2018	ZeJula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	
Venclxyto	venetoclax	05/12/2016		
Verkazia	cielosporina	06/07/2018		
Vyxeos	daunorubicin /cytarabine	23/08/2018		
Xermelo	telotristate	18/09/2017		
Yescarta	axicabtagene ciloleucel	23/08/2018		
Zalmoxis	allogeneic T cells genetically modified with a retroviral vector	18/08/2016		
ZeJula	niraparib	16/11/2017		

The mean difference time to reimbursement was considerably varied, ranging from immediate reimbursement after launch (“real time launch” 94, median 35) days in Germany to 431 (median 415) in Spain, passing through 257 (median 211) in France, 270 (median 265) in the UK and 305 (median 287) in Italy. In the previous analysis, the mean difference time between EMA’s MA and the individual national reimbursement decision ranged from 0 days in Germany (“real time launch” 49 (median 28)) to 277 (median 267) in UK, passing through 217 (median 252) in Italy, 276 (median 276) in Spain and 220 (median 191) in France. By making a comparison between these data, we observed a general prolongation of time to national reimbursement for ODs in the EU5 (except for the UK), due to the longer follow-up and extended data set, longer time frames for the drug assessment, and final registration of the drugs under assessment during the time of the previous analysis.



Even within each single country the ranges between min and max time for reimbursement (days) are highly heterogeneous: 104-562 France; 67-778 Italy; 131-815 Spain; 65-568 UK; and 6-803 Germany (“real time launch” perspective). The min days observed in the previous analysis didn’t change (except from France and Spain, where two different CAR-T products – Kymriah in Spain and Yescarta in France- have been approved in record time). Except for the UK and France, all the max time for reimbursement increased dramatically: +90% in Italy (from 409 to 778), +128% in Spain (from 357 to 815) and +229% in Germany (from 244 to 803). It is important to note that all the three drugs, with the longest time to market are all products commercialized only in very few (1 or 2) countries (Onyvide, Cystadrops and Ledaga). This might be explained by companies’ strategic decisions.

Our study shows, in the last year, a general prolongation on time to national reimbursement for ODs in the EU5, except for the UK. Some countries take more than twice/three time as long as others to reach a decision on reimbursement of new ODs following their approval by the EMA. Wide differences also exist in the available number of reimbursed orphan drugs in the EU5, possibly related to the heterogeneity of assessment procedures applied across Europe.

According to our data, Germany, where reimbursement is automatically granted to all the drugs for which a dossier is submitted in the first year, patients have both the fastest and the most comprehensive access to ODs. France, Italy and Spain show median time to reimbursement of 7, 9,6 and 13,8 months respectively (vs 6, 8 and 9 months, observed in the previous analysis). The United Kingdom shows average values not far from those observed in Italy (8,8 months), despite its theoretical direct access following marketing authorization (this phenomenon can be attributed to an uncertainty-fuelled reluctance on the part of relevant payers in the health system (“Clinical Commissioning Groups” in England and “NHS Boards” in Scotland) to include newly authorized medicines in their formularies before seeing post-marketing evaluation results). Out of Germany, in the other countries between 25% and 77% of ODs are reimbursed. These data show a broaden availability of ODs in the EU5, even without considering available early access schemes (i.e. L 648/96 or L 326/03 in Italy or ATU program in France), which allow several ODs to be made available to patients, even at a very early development stage.

This analysis does not consider the additional time required for regional or local negotiations (Italy and Spain) and the pricing negotiation timing in France. Our analysis is based only on publicly available information and the availability of ODs has been documented using different criteria across the countries included in our analysis.

Further research is required in order to assess both the role of the early access procedure and of drugs’ prices on time to reimbursement for ODsin the EU5.

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