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Analysis of Orphan Drugs Marketed in Spain during the Period 2010-2015: Epidemiological, Clinical and Economic Characteristics

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Abstract

Background: Since the adoption of the European law on orphan drugs in 2000, there has been a significant increase in the number of new therapies for the treatment of rare diseases. The present study aimed to analyse the evidence available on orphan drugs in Spain from 2010-2015 in epidemiological, clinical and economic terms.

Results: During this period, 61 orphan drugs were authorized by the European Commission (EC), of which 44 (72.2%) were authorized in Spain and 19 (31.2%) were finally marketed. The average time from the authorization to commercialization was 527 days. The clinical trials were mostly phase III (57.7%), randomized (79.1%), double-blind (54.2%) and/or open label (43.7%), with half using a placebo (49.9%). Quality-of-life measures were included in 62.4% of the trials and the number of patients in the trials ranged from 14-781. Pharmacological costs were negatively correlated with the prevalence of the diseases. In the absence of systematised economic evaluations in the Spanish setting, the reports published by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) were reviewed and these showed a mean incremental cost-effectiveness ratio (ICER) of £121,072/QALY (quality-adjusted life years).

Conclusion: Orphan drugs marketed in Spain account for one-third of all drugs approved by the EC, with an average time from approval by the EC to commercialization of approximately one and a half years. Clinical trials of orphan drugs have mostly been phase III, randomized, double-blind and/or open label, although in several cases, the number of patients has been limited. An inverse correlation can be observed between the number of patients affected and the monthly pharmacological cost per patient. For 63% of the drugs, the ICERs were above the efficiency threshold.

Keywords: Orphan drug; Prevalence; Clinical trial; Cost-effectiveness ratio; PAS

Background

In the European Union, a rare disease is considered to affect fewer than five patients per 10,000 inhabitants, whereas in the United States, it is defined as affecting fewer than 200,000 patients throughout the entire country, which implies one per every 1,200 inhabitants [1]. Within this group of diseases, ultra-rare diseases are distinguished as those whose prevalence is even lower (one patient per 50,000 inhabitants) [2]. The World Health Organization (WHO) estimates that there are between 5,000 and 7,000 rare diseases, with 250 new ones discovered each year [3] and these affect 7% of the population globally. Despite their low prevalence, rare and ultra-rare diseases together affect approximately 30 million people in the European Union and 3 million in Spain in particular [4]. These diseases often pose a threat to the lives of the affected patients, produce chronic or severe disability and lead to a notable decrease in quality of life.

Orphan drugs are those intended to diagnose, prevent, or treat rare diseases. In 1993, the United States Government and in 2000, the European Union recognised the need to create regulatory mechanisms to encourage the development of orphan drugs [5-7]. Following the implementation of these measures, in the United States, 282 drugs and biological products were approved through 2007, compared to the 10 treatments approved prior to that time [8]. In the European Union, the new regulations elicited a significant increase in the number of drugs marketed, with 60 drugs authorized through 2010 [7].

The increase in the designation of orphan drugs and the associated economic impact are a controversial issue in developed countries, where an economic impact of €265 billion is expected over the next decade, in contrast to the current value of approximately €140 billion [9].

The designation of orphan drugs in the European Union is granted by the European Medicines Agency (EMA), although their funding lies in the health systems of the member countries, which also consider economic criteria [10]. The funding of orphan drugs is a challenge for health care systems because these drugs are often costly and have limited effectiveness [11]. However, in regard to funding orphan drugs, stakeholders generally consider other criteria, such as the severity of the disease, the absence of other therapies for the same disease and the cost to the patient if the medication is not reimbursed by the health care system [12].

There is debate among administrations over these therapies' effectiveness, cost-effectiveness, prevalence and economic impact, which explains the important differences between countries in financing these medicines [13]. The objective of the present study was to describe the evidence available on orphan drugs marketed in Spain from 2010-2015 in epidemiological, clinical and economic terms. Results from this study could contribute to improve the knowledge related to the approval of orphan drugs in Spain and could be of help

for decision-makers when decisions about reimbursement of these drugs have to be made.

Methods

A search for orphan drugs approved by the EMA from January 2010 to December 2015 was performed. For each drug, data were collected on the dates of authorization and commercialization, the existence of conditional approvals, the therapeutic group and the indication. These data were obtained from the official website of the EMA [14]. The date of authorization in Spain was obtained from the Summary of Product Characteristics provided by the Spanish Agency of Medicines and Health Products (AEMPS) [15]. The date of commercialization in Spain was obtained from the Bot PLUS 2.0 database of the Spanish General Council of Official Colleges of Pharmacists (CGCOF) [16]. This information was used to calculate the time from the authorization of the orphan drug by the European Commission (EC) to the authorization in Spain and the time from the authorization in Spain to commercialization.

For the marketed drugs, data on the prevalence of the diseases for which they are indicated were collected using epidemiological data from the periodic report "Orphanet, rare diseases series" [17] and from the ex-factory price of the medicinal products marketed in December 2015 based on the Bot PLUS 2.0 database [16]. The estimates of the monthly pharmacological cost per patient were calculated from the pack costs of the different medicinal products of the orphan drugs and the dosage included in the Summary of Product Characteristics for each medication. For the calculation of drug costs and in the specific situation that the drug dosages are different depending on the patient's weight, m^2 of body surface area, or platelet count, information of the patient profile included as the base case in the economic evaluations published by the Scottish Medicines Consortium (SMC) was considered. For those drugs that had several medicinal products, the calculation was performed using the medicinal products with a lower cost and if the medicine required loading doses and maintenance doses, the calculation used the monthly cost for the maintenance doses.

The populations affected by rare diseases in Spain in 2015 were estimated using data on the Spanish population as of January 1, 2015, which were collected by the Spanish National Institute of Statistics (INE) [18] and data on the prevalence of these diseases.

Furthermore, the orphan drugs authorized in Spain during the period evaluated were selected for an analysis of the characteristics of the clinical trials that served as the basis for their authorization. Data were collected on the phase and design of each trial, the comparator used, the number of patients, the duration of the study and the inclusion of instruments to measure the patients' quality of life. The data were obtained from the evaluation reports published on the official website of the EMA [14].

Due to the absence of an organisation that systematically conducts national economic assessments in Spain, international data were used. Information was specifically collected from the National Institute for Health and Care Excellence (NICE) and from the SMC. The type of economic evaluation performed, the value of the incremental cost-effectiveness ratio (ICER), the existence of specific agreements to guarantee access to the drug and the final recommendation decision by the agency were identified. The ICER values from these reports were recorded as £/QALY (quality-adjusted life years) for the base case corresponding to the year in which the respective report was published.

Results

From January 2010 to December 2015, the EC authorized 56 orphan drugs with 61 orphan indications. Hereafter, the term "orphan drug" will be used to refer to both orphan drugs and orphan indications. Of these drugs, 44 (72.1%) were authorized for commercialization in Spain and 19 (31.2%) were finally marketed. The mean time from EC approval to authorization in Spain was 181 days (median: 81 days, range: 14 to 916 days) and the mean time from EC approval to commercialization in Spain was 527 days (median: 493 days, range: 124 to 1,032 days) (Table 1).

Of all the orphan drugs authorized in Europe during this period, 34 (56%) had some type of approval restriction due to the establishment of special authorization requirements. Conditional approvals based on monitoring of the efficacy and safety of the drug and provision of this information at annual intervals were the most requested, totalling 11 (32.4%) approvals. Authorization under exceptional circumstances wherein annual monitoring was also requested occurred in five of the approvals (14.6%). For the remaining 18 (53%) approvals, other types of studies were requested, or more specific restrictions were imposed (Table 1).

Figure 1 shows the therapeutic areas of the orphan drugs that were designated by the EMA, those that were authorized in Spain and those that were finally marketed during the 2010-2015 period. The most common therapeutic group was antineoplastic drugs, accounting for 37.7%, 50% and 57.9% of the European designations, Spanish authorizations and commercializations, respectively. The next most common groups in terms of European designations and Spanish authorizations were gastrointestinal and metabolic drugs (13.1% and 9.1%, respectively), although these numbered well below the antineoplastics.

An average of 1.3 clinical trials were performed per orphan drug to obtain approval authorization (Table 1 Supplementary Information). Figure 2 shows the temporal evolution of the approvals and commercializations that occurred during the study period. Increasing trends were observed across time with regard to the number of drugs that obtained the orphan designation, those that were authorized in Spain and those that were finally marketed.

Table 2 shows the characteristics of the clinical trials performed with orphan drugs authorized in Spain during the 2010-2015 period, classified by therapeutic area and totalled. Of the clinical trials, 57.7% were conducted as phase III trials, with the majority being randomized (79.1%), double blind (54.2%) and/or open label (43.7%).

Most trials used a placebo as a comparator (49.9%), followed by those without an active comparator (27%) and then by those with an active comparator (20.8%).

The clinical trials most commonly had a sample size of 50 to 249 patients (41.6%), with a size of 250 to 500 patients being second most common (27%). In 12.5% of the studies, there were fewer than 50 patients. The mean sample size of the trials was 260 patients.

Studies with a duration of up to 6 months accounted for 31.2% of the studies sampled. However, the duration of clinical trials depended on the type of disease. For example, in the case of antineoplastics, the majority of the trials were extended through the progression of the disease or until unacceptable toxicity (57.8%), without defining a specific period.

Drug	Brand	Indication (therapeutic group)	Authorization EC	Authorization in Spain	Commercialization in Spain	Restriction in the Authorization	Until authoris. Spain (Days)	Until commercialization (Days)	Total days
Glycerol phenylbutyrate	Ravicti	Hereditary disorders of the urea cycle (Gastrointestinal and metabolic)	27-11-2015	No	No	Registry of patients to obtain further information of long-term benefits and safety	-	-	-
Blinatumomab	Blincyto	Acute lymphoblastic leukaemia (Antineoplasic)	23-11-2015	16-12-2015	No	Conditional approval: study of effectiveness and safety	23	-	23
Colic acid	Kolbam	Hereditary lack of bile acids (Hepatic)	20-11-2015	No	No	No	-	-	-
Carfilzomib	Kyprolis	Multiple myeloma (Antineoplasic)	19-11-2015	04-12-2015	No	No	15	-	15
Efmoroctocog alfa	Elocta	Haemophilia A (Injection)	19-11-2015	No	No	No	-	-	-
Lumacaftor/ Ivacaftor	Orkambi	Cystic fibrosis (Pulmonar)	19-11-2015	No	No	No	-	-	-
Isabuconazole	Cresemba	Aspergillosis (Infections)	15-10-2015	No	No	No	-	-	-
Idebenone	Raxone	Hereditary optic neuropathy (Central Nervous System)	08-09-2015	No	No	Exceptional circumstances: Long-term efficacy and safety data	-	-	-
Sebelipase alfa	Kanuma	Lysosomal acid lypase deficiency (Gastrointestinal and metabolic)	28-08-2015	No	No	Registry of patients to set a long-term safety study by age subgroups	-	-	-
Asfotase alfa	Strensiq	Hypophosphatasia (Gastrointestinal and metabolic)	28-08-2015	15-10-2015	No	Exceptional circumstances: Long-term efficacy and safety data	48	-	48
Panobinostat	Farydak	Multiple myeloma (Antineoplasic)	28-08-2015	22-12-2015	No	No	116	-	116
Dinutuximab	Unituxin	Neuroblastoma (Antineoplasic)	14-08-2015	No	No	No	-	-	-
Tasimelteon	Hetlioz	Cardiac and sleep disorder (Psycoleptic)	03-07-2015	No	No	No	-	-	-
Lenvatinib	Lenvima	Differenciated thyroid carcinoma, refractory to radioactive iodine (Antineoplasic)	28-05-2015	02-10-2015	No	Conditional approval: annual monitorization	127	-	127
ex vivo human corneal Epitel.Cel. Stem	Holoclar	Deficiency in limbal stem cell (Oftalmologic)	17-02-2015	16-09-2015	No	No	211	-	211
Eliglustat	Cerdelga	Gaucher disease (Gastrointestinal and metabolic)	19-01-2015	No	No	Long-term safety study without certain drugs	-	-	-
Nintedanib	Ofev	Idiopatic pulmonar fibrosis (Immunosuppresant)	15-01-2015	09-03-2015	11-12-2015	No	53	277	330
Afamelanotide	Scenesse	Prevention of photoxicity with erythropoietic protoporphyria (Emollient and protective)	22-12-2014	No	No	Exceptional circumstances: annual monitorization	-	-	-
Ramucirumab	Cyramza	Gastric cancer and adenocarcinoma of the gastroesophagic joint (Antineoplasic)	19-12-2014	16-02-2015	01-12-2015	No	59	288	347
Olaparib	Lynparza	Cancer of the ovary, fallopian tubes and cancer of the peritoneum sesitive to platin with BRCA gene mutations (Antineoplasic)	16-12-2014	04-02-2015	No	Long-term safety study	50	-	50
Ketoconazol	Ketoconazole HRA	Cushing's syndrome (Hormonal)	19-11-2014	No	No	No	-	-	-
Ibrutinib	Imbruvica	Chronic lymphocitic leukaemia with genetic mutations in TP53 or have received at least one previous treatment (Antineoplasic)	21-10-2014	06-11-2014	No	Benefits information	16	-	16
Ibrutinib	Imbruvica	Mantle cell lymphoma without response to other treatment or come back (Antineoplasic)	21-10-2014	06-11-2014	No	Study comparing with temsirolimus	16	-	16
Ataluren	Translarna	Duchenne muscular dystrophy (Muscular)	31-07-2014	01-12-2014	No	Conditional approval: efficacy and safety aditional data	123	-	123
Obinutuzumab	Gazyvaro	Chronic lymphocytic leukaemia without previous treatment and comorbidities for which fludarabine is not recommended (Antineoplasic)	23-07-2014	06-08-2014	19-10-2015	No	14	439	453
Siltuximab	Sylvant	Castleman's disease negative for VIH and HVH-8 (Immunosuppresant)	22-05-2014	24-10-2014	No	Registry of patients to obtain further information of long-term benefits and safety	155	-	155
Delamanid	Deltyba	Multiresistant tuberculosis (Infections)	28-04-2014	No	No	Conditional approval: study of long-term effectiveness and safety data	-	-	-
Elosulfase alfa	Vimizim	Mucopolysaccharidosis type IVA in all patients. (Gastrointestinal and metabolic)	28-04-2014	23-03-2015	No	Registry of patients to obtain further information of long-term benefits and safety	329	-	329
4-Aminosalicyl. acid	Granupas	Multiresistant tuberculosis (Infections)	07-04-2014	No	No	No	-	-	-
Riociguat	Adempas	Cronic pulmonary tromboembolic hypertension (Pulmonar)	27-03-2014	21-05-2014	19-05-2015	No	55	363	418
Cabozantinib	Cometriq	Medullary thyroid cancer progresive, no resectable, locally advanced or metastasic (Antineoplasic)	21-03-2014	24-03-2015	No	Conditional approval: annual monitorization	368	-	368
Bedaquiline	Sirturo	Multiresistant tuberculosis (Infections)	05-03-2014	18-09-2014	No	Conditional approval: annual monitorization	197	-	197
Macitentan	Opsumit	Pulmonary arterial hypertension (Pulmonar)	20-12-2013	07-05-2014	01-06-2015	Not in pregnant women or who could become pregnant	138	390	528
Defibrotide	Defitelio	Severe veno-occlusive disease (Antitrombotic)	18-10-2013	No	No	Exceptional circumstances: long-term monitorization of eficacy, health and use results	-	-	-
Mercaptamine	Procysbi	Nephropathic cystosis (Gastrointestinal and metabolic)	06-09-2013	No	01-09-2014	Not to alergic to mercaptamina, penicyalminas or lactans	-	-	-
Colic acid	Orphacol	Hereditary deficiency of bile acids (Hepatic)	02-09-2013	15-01-2015	No	Data base to evaluate eficacy and safety in intervales	500	-	500
Pomalidomida	Imnovid	Multiple myeloma (Immunosuppresant)	05-08-2013	20-12-2013	13-06-2014	Pregnancy prevention programme	137	175	312
Ponatinib	Iclusig	Chronic myeloid leukaemia resistant or intolerant to desatinib or nilotinib and for the subsequent treatment with imatinib or the mutation T315I. (Antineoplasic)	01-07-2013	20-09-2013	No	Study for the best starting dose, and the eficacy and safety following dose reduction	81	-	81
Bosutinib	Bosulif	Acute lymphoblastic leukaemia Ph+ (Antineoplasic)	01-07-2013	20-09-2013	No	No	81	-	81
Bromelain	NexoBrid	Deep partial-thickness and full-thickness burns (Dermatologic)	18-12-2012	15-09-2014	No	Conditional approval: annual monitorization	636	-	636+
Alipogen tiparvovec	Glybera	Lipoprotein-lipase deficiency (Lipid modifying agents)	25-10-2012	10-10-2014	No	Log-term comparative study in adults and children	715	-	715
Brentuximab	Adcetris	Chronic lymphoblastic leukaemia Ph+ with tyrosin kinase inhibitors and not treated with imatinib, nilotinib and desatinib. (Antineoplasic)	25-10-2012	29-11-2012	01-08-2014	Conditional approval: annual monitorization	35	610	645
Brentuximab	Adcetris	Anaplasic lymphoma of large cells and Hodgkin lymphoma (Antineoplasic)	25-10-2012	29-11-2012	01-08-2014	Conditional approval: annual monitorization	35	610	645
Decitabine	Dacogen	Acute myeloid leukaemia (Antineoplasic)	30-08-2012	28-05-2013	01-09-2014	Not alergic to decitabine	271	461	732
Teglutide	Revestive	Short bowel syndrome (Gastrointestinal and metabolic)	30-08-2012	29-05-2013	No	Registry of patients to studies of effectiveness and safety	81	-	81
Ruxolitinib	Jakavi	Primary myelofibrosis (Antineoplasic)	23-08-2012	12-11-2012	12-01-2015	No	81	791	872
Ruxolitinib	Jakavi	Post-polycythemia vera myelofibrosis (Antineoplasic)	23-08-2012	12-11-2012	12-01-2015	Long-term effectiveness and safety studies	81	791	872
Ruxolitinib	Jakavi	Post-essential trombocythaemia myelofibrosis (Antineoplasic)	23-08-2012	12-11-2012	12-01-2015	No	81	791	872
Ivacaftor	Kalydeco*	Cystic fibrosis with 9 mutations in CFTR gene (Pulmonar)	23-07-2012	11-06-2013	No	Long-term safety study	323	-	323+
Pasireotide	Signifor	Cushing's disease after surgery failure (Hormonal)	24-04-2012	28-05-2012	No	No	34	-	34
Mannitol	Bronchitol	Cystic fibrosis (Pulmonar)	13-04-2012	No	No	No	-	-	-
Mercaptopurine	Xaluprine	Accute lymphoblastic leukaemia (Antineoplasic)	09-03-2012	05-02-2013	No	No	333	-	333
Tafamidis	Vyndaqel	Transthyretin amyloidosis in adults with polyneurophaty stage 1 (Central Nervous System)	16-11-2011	30-11-2011	01-12-2013	Conditional approval: annual monitorization	14	732	746
Hydrocortisone	Plenadren	Adrenal insufficiency (Hormonal)	03-11-2011	07-05-2014	No	No	916	-	916
Everolimus	Votubia	Udependymal giant cell astrocytoma and renal angiomyolipoma (Antineoplasic)	02-09-2011	28-09-2011	24-06-2014	Conditional approval: annual monitorization	26	635	661
Tobramycin	Tobi Podhaler	Infection by bacteria called P. aeruginosa in cystic fibrosis (Infections)	20-07-2011	12-08-2011	17-12-2012	Conditional approval: annual monitorization	23	493	516
Pirfenidone	Esbriet	Idiopatic pulmonar fibrosis (Immunosuppresant)	28-02-2011	04-11-2011	01-09-2014	Study of safety and adverse events	249	1032	1281
Velaglucerase alfa	Vpriv	Type 1 Gaucher disease (Gastrointestinal and metabolic)	26-08-2010	28-10-2010	01-03-2011	No	63	124	187
Ofatumumab	Arzerra	Chronic lymphoid leukaemia linfocítica in adults resistant to fludarabina and alemtuzumab (Monoclonal antibody)	19-04-2010	07-06-2012	01-07-2014	Conditional approval: annual monitorization	780	754	1534
Tiotepa	Tepadina	Hematopoyetic cell transplantation (Antineoplasic)	15-03-2010	29-10-2010	07-07-2011	No	228	251	479

Table 1: Orphan drugs approved by CE, and authorized and commercialized in Spain.

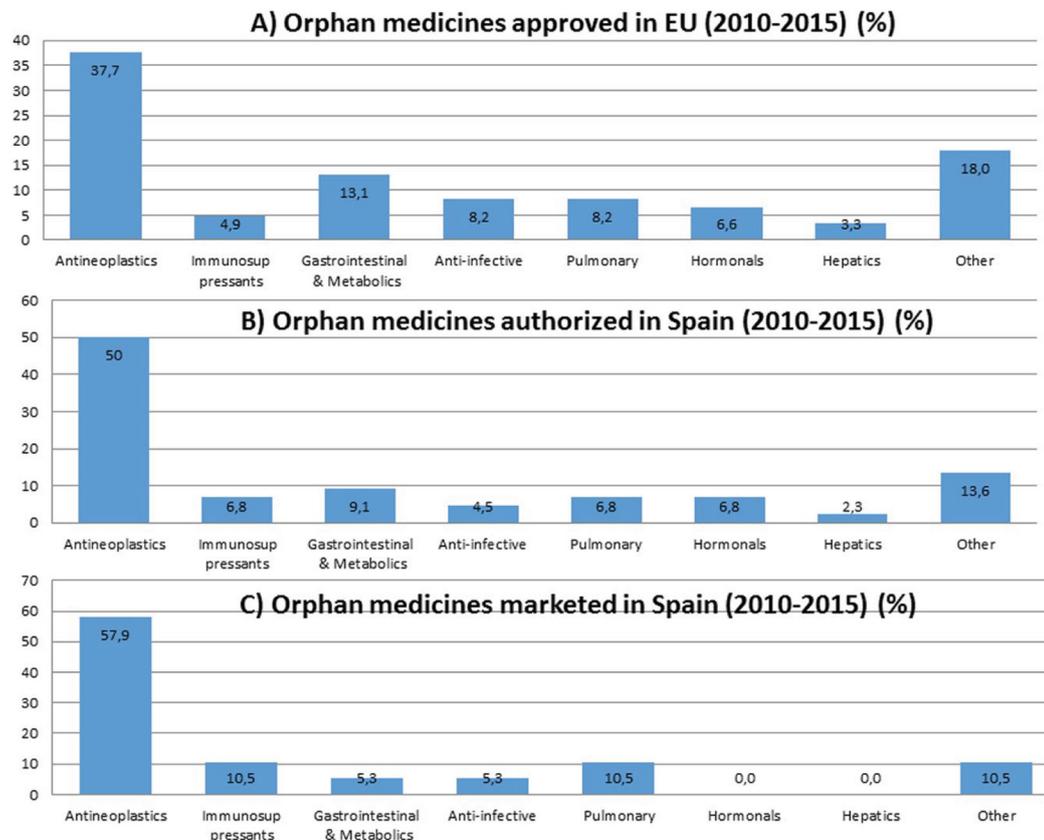*Days to commercialization in Spain is unknown

Figure 1: Distribution of the orphan drugs from 2010-2015 by therapeutic area. A) EU authorization; B) Spanish authorization and C) Spanish commercialization. "N" is the number of orphan drugs and "(%)" is the percentage of the therapeutic area.
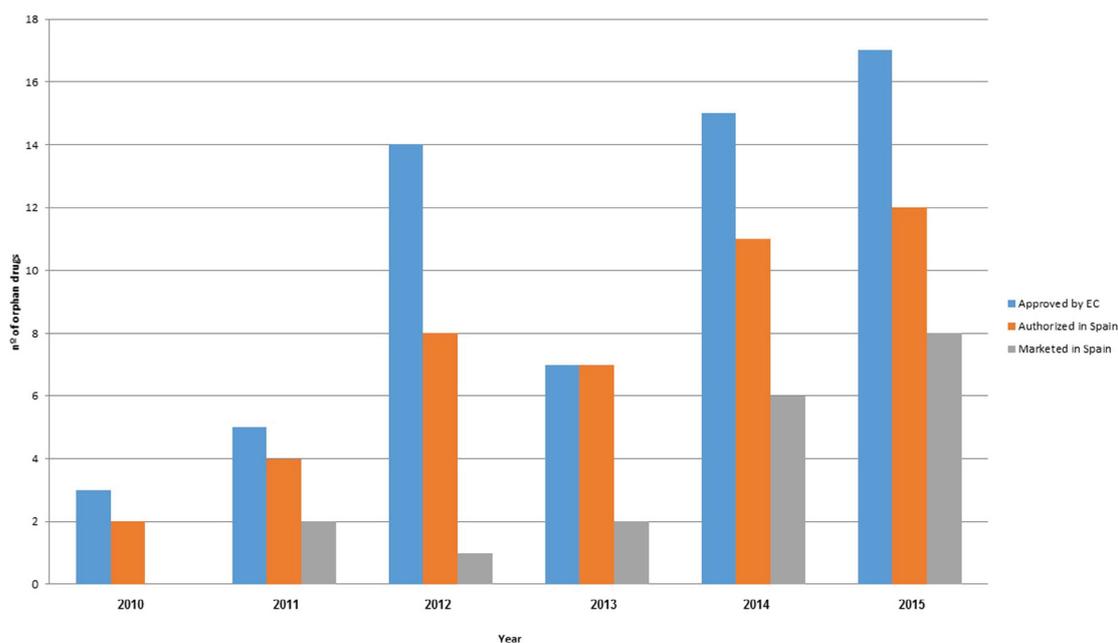

Figure 2: Annual number of orphan drugs from 2010-2015. Authorized by the EC and authorized and commercialized in Spain.

	Antineoplastics	Gastrointestinal and metabolics	Immunosuppresants	Anti-infective	Pulmonary	Hormonals	Hepatics	Others	TOTAL
Number of the orphan drugs	17	4	4	2	3	2	1	6	39
Number of the clinical trials	21	5	6	3	5	3	1	8	52
Type	21 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	3 (100%)	1 (100%)	8 (100%)	52 (100%)
Phase I/II	1 (4.7%)								1 (1.9%)
Phase II	7 (33.3%)		1 (16.6%)	1 (33.3 %)		1 (33.3 %)		2 (25%)	11 (21.11%)
Phase II/III						1 (33.3 %)		1 (12.5%)	2 (3.8%)
Phase III	11 (52.3%)	3 (60%)	5 (83.3%)	2 (66.6%)	5 (100%)	1 (33.3 %)		1 (12.5%)	28 (53.8%)
Scientific literature	2 (9.5%)						1 (100%)		4 (7.6%)
Study to Determine the Safety and Efficacy		2 (40%)						3 (37.5%)	5 (9.6%)
Retrospective evaluation								1 (12.5%)	1 (1.9%)
Design	19 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		8 (100%)	48 (100%)
Randomized	12 (63.15%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		5 (62.5%)	38 (79.1%)
Non Randomized	2 (10.5%)							1 (12.5%)	3 (6.25%)
Single arm	4 (21%)							1 (12.5%)	5 (10.4%)
Retrospective evaluation								1 (12.5%)	1 (2%)
Cohort study	1 (5.2%)								1 (2%)
Double-blind	7 (36.8%)	4 (80%)	5 (83.3%)	2 (66.6%)	5 (100%)	1 (50%)		2 (28.5%)	26 (54.16%)
Open-label	12 (63.1%)	1 (20%)	1 (16.6%)	1 (33.3 %)		1 (50%)		5 (71.4%)	21 (43.7%)
Retrospective evaluation								1 (12.5%)	1 (2%)
Comparators	19 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		8 (100%)	48 (100%)
Placebo	7 (36.8%)	3 (60%)	3 (50%)	2 (66.6%)	5 (100%)			2 (25%)	22 (45.8%)
Placebo and low doses of drug			2 (33.3%)						2 (4.1%)
Active comparator	4 (21%)	1 (20%)	1 (16.6%)					1 (12.5%)	7 (14.5%)
Not comparator	6 (31.5%)							3 (37.5%)	9 (18.7%)
Dose escalation regimen				1 (33.3 %)		1 (50%)		2 (25%)	4 (8.3%)
Replacement therapy						1 (50%)			1 (2%)
Best Available Therapy	2 (10.5%)								2 (4.1%)
'Historical controls'		1 (20%)							1 (2%)
Number of patients	19 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		8 (100%)	48 (100%)
Less than 50	1 (5.2%)	2 (40%)						3 (37.5%)	6 (12.5%)
50-249	5 (26.3%)	3 (60%)	1 (16.6%)	2 (66.6%)	2 (40%)	2 (100%)		5 (62.5%)	20 (41.6%)
250-500	8 (42.1%)		3 (50%)		2 (40%)				13 (27%)
More than 500	5 (26.3%)		2 (33.3%)	1 (33.3 %)	1 (20%)				9 (18.7%)
Duration	19 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		8 (100%)	48 (100%)
Until 6 months	2 (10.5%)	4 (80%)	1 (16.6%)	3 (100%)	3 (60%)	1 (50%)		1 (12.5%)	15 (31.2%)
Until 12 months	1 (5.2%)	1 (20%)	2 (33.3%)		2 (40%)	1 (50%)		4 (50%)	11 (22.9%)
More 12 months	4 (21%)		2 (33.3%)					3 (37.5%)	9 (18.7%)
Until progressive disease or unacceptable toxicity	11 (57.8%)		1 (16.6%)						12 (25%)
Patients benefited from treatment	1 (5.2%)								1 (2%)
Quality-of-life evaluation	19 (100%)	5 (100%)	6 (100%)	3 (100%)	5 (100%)	2 (100%)		8 (100%)	48 (100%)
Not present	6 (31.57%)	1 (20%)	1 (16.6%)	2 (66.6%)	3 (60%)			5 (62.5%)	18 (37.5%)
Favorable	4 (21%)	2 (40%)						1 (12.5%)	7 (14.5%)
Neutral	6 (31.57%)				2 (40%)				8 (16.6%)
Inconclusive	3 (15.7%)	2 (40%)	5 (83.3%)	1 (33.3 %)		2 (100%)		2 (25%)	15 (31.25%)

Table 2: Characteristics of the clinical trials of orphan drugs authorized in Spain from 2010-2015.

Drug	Indication	Prevalence (x10,000hab)	Target population	Estimation of n° of cases in Spain (2015)	Pack	Manufacture Selling Price (Decem. 2015)	Estimation of the monthly pharmacological cost per patient (Month 30.4 days)	Posology
Nintedanib	Idiopatic pulmonar fibrosis	3	Adult population	11,431	100 mg (60 tablets) / 150 mg (60 tablets)*	2,403.85 €	2,435.90 €	150 mg twice a day
Ramucirumab	Gastric cancer and adenocarcinoma of the gastroesophagic joint	3	Adult population	11,431	10 mg/ml (1 vial 10 ml)* / 10 mg/ml (1 vial 50 ml)*	597 € / 2,985 €	7,259.52 €	8 mg per kg body weight given on days 1 and 15 of a 28-day cycle (mean weight: 75 kg)
Obinutuzumab	Chronic lymphocytic leukaemia	3	Adult population	11,431	10000 mg (1 vial/40 ml)	3,970 €	4,310.28 €	For the remaining cycles, a dose of 1,000 mg is given on day one only (cycle 28 days)
Riociguat	Chronic pulmonary tromboembolic hypertension	2	Adult population	7,621	1mg (42 tablets) / 1.5 mg(42 tablets) / 2mg (42 tablets) / 2.5 mg (42 tablets)	1,260 €	2,736 €	1 mg three times a day for two weeks. The dose is then increased every two weeks until the appropriate dose for the individual patient is established. The maximum dose should not exceed 2.5 mg three times a day (All dose, the same monthly pharmacological cost per patient)
Macitentan	Pulmonary arterial hypertension	1.8	Adult population	6,858	10 mg (30 tablets)	2,450 €	2,482.67 €	10 mg once day
Pomalidomide	Multiple myeloma	2.2	Adult population	8,383	3 mg (21 caps.) / 4 mg (21 caps.)*	9,300 €	10,097.14 €	4 mg once a day, taken at the same time each day for the first three weeks of the cycle, followed by a week of no treatment
Brentuximab	Chronic lymphoblastic leukaemia	1	Adult population	3,810	50 mg (1 vial)	3,300 €	11,774.54 €	1.8 mg per kg every three weeks (mean weight: 75 kg)
	Anaplastic lymphoma of large cells and Hodgkin lymphoma	0.2	Adult population	762			9,673.72 €	
Decitabine	Acute myeloid leukaemia	0.35	Adult patients aged 65 years	301	50 mg (1 via)	1,111.05 €	4,101.36 €	20 mg per m2 surface area per day (Mean body surface area: 1,7m2)
Ruxolitinib	Primary myelofibrosis	0.5	Adult population	1,905	5 mg (56 tablets) / 10 mg (56 tablets)* / 15 mg (56 tablets)*	1,791.66 € / 3,583.33 € / 3,583.33 €	3,890.47 €	15 mg two times a day (SMC)
	Post-polycytaemia vera myelofibrosis	5	Adult population	19,051			3,890.47 €	
	Post-essential trombocythaemia myelofibrosis	0.01	Adult population	38			3,890.47 €	
Tafamidis	Transthyretin amyloidosis	0.1	Adult population	381	20 mg (30 caps.)	11,100 €	11,248 €	20 mg once a day
Everolimus	Ubependymal giant cell astrocytoma and renal angiomyolipoma	1	Adult population	3,810	2 mg (30 tablets) / 2.5 mg (30 tablets) / 5 mg (30 tablets) / 10 mg (30 tablets)*	1,013.42 € / 1,266.78 € / 2,533.75 € / 3,300,97 €*	3,344.98 €	In patients with renal angiomyolipoma, 10 mg once a day
Tobramycin	Infection by bacteria called P. aeruginosa in cystic fibrosis	1.3	Patients aged 6 years and older	5,681	28 mg (224 caps.)	2,243.33 €	4,486.60 €	112 mg twice a day for four weeks, followed by four weeks without treatment
Pirfenidone	Idiopatic pulmonary fibrosis	3	Adult population	11,431	267 mg (63 tablets) / 267 mg (252 tablets)*	600.96 € / 2,043.85 €	2,609.89 €	801 mg three times a day (2,609.89 € in subsequent months)
Velaglucerase alfa	Type 1 Gaucher disease	0.3	Patients aged 4 years and older	1,340	400 UI (1 vial)	1,409.54 €	34,433.05 €	60 units/kg, once every two weeks (Mean wright: 75 kg)
Ofatumumab	Chronic lymphoid leukaemia linfocitica	3.5	Adult population	13,336	100 mg (3 vials/5 ml)* / 1000 mg (1 vial/50 ml)*	648.90 € / 2,163 €	2,163 €	The first infusion should contain 300 mg on day 1, followed 7 days later by 1,000 mg. All subsequent infusions (which should be between 2 and 11 more infusions) should contain 1,000 mg given once a month. (2,163 € in subsequent infusions)
Thiotepa	Hematopoyetic cell transplantation	0.6	Adult and pediatric population	2,680	15 mg (1 vial) / 100 mg (1 vial)*	135 € / 810 €	8,778.37 €	In adults, the daily dose ranges from 125 to 300 mg per m2 administered from 2 up to 4 consecutive days before transplantation (Mean body surface area: 1,7m2)

Table 3: Prevalence, target population, estimation of the prevalence in Spain and estimation of the monthly pharmacological cost per patient.

The quality of life of the patients was measured in 62.4% of the trials. The result of this evaluation was inconclusive in 31.3%, neutral in 16.6% and favourable in only 14.5%.

Table 3 shows the prevalence for the rare diseases, the estimated population affected by these diseases in Spain in 2015 and the medicinal products and ex-factory price of each drug as well as the estimated monthly pharmacological cost per patient for the drugs marketed in Spain during the period evaluated. The estimated number of patients in Spain with a rare disease for which an orphan drug was marketed was 121,591. Among them, 19,051 patients had post-polycythaemia vera myelofibrosis and 38 patients had post-essential thrombocythaemia myelofibrosis, which had the highest and lowest prevalence, respectively. Moreover, the monthly pharmacological cost per patient ranged from €34,433 for velaglucerase alfa to €2,163 for ofatumumab, with an average cost of €7,032 for all the drugs.

Figure 3 shows the correlation between the estimated monthly pharmacological cost per patient and the prevalence of the disease. In general terms, the estimated monthly pharmacological cost was higher when the prevalence of the disease was lower and vice versa.

The NICE and SMC economic evaluation reports of the orphan drugs marketed in Spain between 2010 and 2015 are shown in Table 4. During this period, the SMC prepared 16 reports, whereas the NICE prepared 7. The ICERs of the study drugs in these reports ranged from −£13,295 to £1,232,645/QALY, with a mean ICER of £121,072/QALY for all the study drugs. ICERs below the threshold of £20,000-30,000/QALY were found in 36.8% of the evaluations [19]. With respect to the occurrence of some mode of a patient access scheme (PAS)-type agreement in the evaluations, 70% of them considered a final PAS after knowing the value of the ICER, whereas 47.4% procured a PAS agreement before the calculation of the ICER.

The final recommendations provided by the corresponding evaluating agencies were positive in 65.2% of the reports, compared to 34.8% negative. Of the latter, 37.5% were negative because economic information was not provided to the evaluating organisation.

Only one orphan drug (NexoBrid®) marketed in Spain during this period was not reported on by the two organisations.

Discussion

The European regulation on orphan drugs established in 2000 (141/2000) [7] has encouraged the development of therapies for rare diseases, which has in turn led to an increase in the number of authorizations [20]. Since that year, there has been a continued increase in the number of new authorizations for orphan drugs in Europe [7]. The results of the present study indicate that this growing trend continued through 2015. Despite the incentivising regulation, only 31.2% of the drugs authorized by the EC during this period were marketed in Spain. In addition, the waiting period until commercialization was very long, with an average of more than 500 days, meaning nearly a year and a half elapsed before the drugs could be marketed. These results are in line with other Spanish studies that determined that the period from approval by the EMA to the first prescription is 24 months [21].

In more than half of the cases (56%) in the current analysis, EC approvals of orphan drugs considered some type of conditional or exceptional circumstances. These approvals were mostly related to the small population of patients who participated in the clinical trials and always related to the prevalence of the disease and the measures of effectiveness achieved. This finding demonstrates that health

authorities positively value the discovery of effective drugs to treat cancer and that they are open to authorization based on early positive data [22]. The results additionally show that oncological drugs were much more often authorized than other therapeutic groups during the study period in Europe in general and in Spain in particular. This finding has also been observed in other studies [5,6,23]. The reason that this area is better developed may be that new diagnostic techniques can differentiate among different subtypes of cancer, thereby allowing orphan designation of low-prevalence subtypes [24]. Moreover, in the area of oncology, drugs are used to alleviate disease, such that the potential benefits can be very high because they imply patient survival, whereas in other rare diseases, drug administration is chronic and only produces limited improvement of the disease [25].

The majority of the clinical trials of orphan drugs approved in Spain were phase III (57.7%), randomized (79.1%) and/or double blind (54.2%), differing little from non-orphan drug trials in terms of the methodologies used [26,27].

The numbers of patients participating in the trials were low, meaning that it was challenging to obtain robust evidence regarding efficacy and safety and these numbers were quite different from the sample sizes observed in clinical trials of non-orphan drugs [27].

There was an increasing tendency to evaluate the quality of life of the patients in the clinical trials (62.4%), in contrast to other series studied [28]. This trend reflects the growing intention to provide evidence in this area, which is so important for rare diseases, where an increase in quality of life is often as important as achieving high treatment efficacy [29].

In recent years, the annual pharmaceutical budget for orphan drugs, accounting for 2.5% of spending in 2007 and 3.3% in 2010, with an upward prediction of 6.6% for 2020 [9,20]. This increase represents a challenge for ensuring the sustainability of health care systems. The present study shows that orphan drugs marketed in Spain for rare diseases with a lower prevalence are associated with higher pharmacological costs. This trend has already been described previously [10,23,30,31]. Even so, the calculation of the number of patients in Spain based on prevalence data for rare diseases and the general population of Spain may be obtained more reliably with the recent creation of a registry that includes the number of people affected in the country [32].

Economic evaluations are tools that help with health decision-making by identifying interventions that produce the greatest health outcomes with the given resources. In Spain, there is no organisation that systematically evaluates the efficiency of drugs. The current study therefore analysed information from the economic evaluations issued by two institutions in the United Kingdom that are pioneers in evaluating efficiency and that serve as models for countries where routine evaluations are not yet available. The ICER data from the evaluation reports showed a wide range (−£13,295 to £1,232,654/QALY), which coincides with the findings of another published study [33].

Of the evaluations, 36.8% had ICER values that would be considered efficient according to the NICE criterion [19], although in general, it is thought that these drugs are not cost-effective [12].

Strategies have been developed in recent years to help health decision-makers evaluate the effects of new oncology drugs under the conditions of daily clinical practice [34]. The evaluation of effectiveness [35], linked to PAS-type agreements, has become increasingly more common in recent years. The presence of PAS-type agreements for

Organization	Drug	Brand	Year	Indication	Costs included	Perspective	Evaluation	Sensitivity analysis	ICER £/QALY	ICER PAS (included in ICER)	PAS (final)	Recommendation
SMC	Obinutuzumab	Gazyvaro	2014	Lymphiod leukaemia	Health care costs	Health care system	Cost-Utility	YES	22,568-28,428	NO	NO	YES
NICE	Ramucirumab	Cyramza	2016	Gastric cancer	Health care costs	Health care system	Cost-Effectiveness	YES	188,640-118,209	NO	NO	NO
NICE	Nintedanib	Ofev	2016	Pulmonary fibrosis	Health care costs	Health care system	Cost-Effectiveness	YES	149,361	NO	YES	YES
SMC			2015		Pharmacological costs	Health care system	Cost-Utility	YES	-	-	YES	YES
SMC	Riociguat	Adempas	2014	Chronic pulmonary tromboembolic hypertension	Health care costs	Health care system	Cost-Utility	YES	-13,295	YES	YES	YES
SMC	Macitentan	Opsumit	2014	Pulmonary arterial hypertension	Health care costs	Health care system	Cost minimization	NO	61,008	NO	YES	YES
NICE	Pomalidomide	Imnovid	2015	Multiple Myeloma	Health care costs	Health care system	Cost-Utility	YES	50,366, 77,915 72,250 *	YES	NO	NO
SMC			2014		Health care costs	Health care system	Cost-Utility	YES	33,716	YES	YES	YES
SMC	Brentuximab	Adcetris	2014	Hodgkin disease lynphoma	Health care costs	Health care system	Cost-Utility	YES	43,731	NO	NO	YES
SMC	Decitabine	Dacogen	2013	Myeloid leukaemia	No reported	No reported	No reported	No reported	No reported		No reported	NO
NICE	Ruxolitinib	Jakavi	2013	Myelofibrosis, polycythaemia vera	Health care costs	Health care system	Cost-Utility	YES	73,980	NO	NO	NO
SMC			2015		Health care costs	Health care system	Cost-Utility	YES	49,774	YES	YES	YES
SMC	Ivacaftor	Kalydeco	2013	Cyistic fibrosis with mutations in CFTR gene	Pharmacological cost	Health care system	Cost-Utility	YES	277,011	YES	YES	NO
SMC	Tafamidis**	Vyndaqel	2013	Amyloidosis	No reported	No reported	No reported	No reported	No reported		No reported	NO
SMC	Everolimus**	Votubia	2013	Astrocytoma	No reported	No reported	No reported	No reported	No reported		No reported	NO
NICE	Tobramycin	Tobi Podhaler	2013	Infection of *P. aeruginosa* in cystic fibrosis	Health care costs	Health care system	Cost-Effectiveness	YES	123,563	NO	YES	YES
SMC			2012		Pharmacologic cost	Health care system	Cost minimization	NO	11,675	NO	YES	YES
NICE	Pirfenidone	Esbriet	2013	Idiopatic pulmonary fibrosis	Health care costs	Health care system	Cost-Effectiveness	YES	36,327	YES	YES	YES
SMC			2013		Health care costs	Health care system	Cost-Utility	YES	27,575	YES	YES	YES
SMC	Velaglucerase alfa	Vpriv	2012	Type 1 Gaucher disease	Pharmacological cost	Health care system	Cost minimization	NO	1,232,645	NO	YES	YES
NICE	Ofatumumab	Arzerra	2015	Lynphoid leukaemia	Health care costs	Health care system	Cost-Utility	YES	23,414	YES	YES	YES
SMC			2015		Health care costs	Health care system	Cost-Utility	YES	28,813	YES	YES	YES
SMC	Tiotepa	Tepadina	2012	Hematopoyetic cell transplantation	Pharmacological cost	Health care system	Cost-Utility	YES	3,426-4,110	NO	NO	NO

*50,366 comparation with bortezomib+dexametasona, 77,915 comparation with talidomida+dexametasona and 72,250 comparation with bendamustina+talidomida and dexametasona.
***No reported"; pharmacoeconomic information was not provided to the evaluating organization and there is not a recommendation.

Table 4. Economic evaluation reports from NICE and SMC in marketed orphan drugs in Spain.
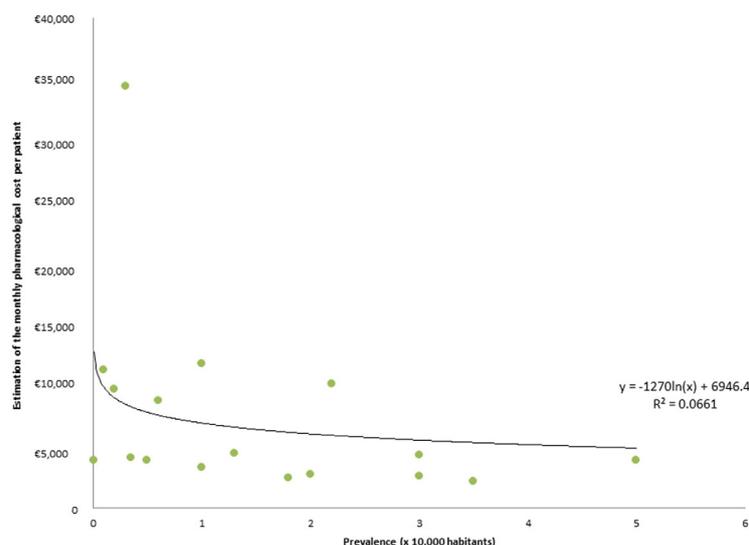
Figure 3: Monthly pharmacological cost per patient and estimated prevalence of rare diseases.

the recommendation of positive financing for the drugs included in this study highlights the importance of these payment strategies for reaching agreements on orphan drugs [34].

In Spain, health authorities have a growing concern about the impact of rare diseases in the population in terms of costs and quality of life. As an example, the Spanish Ministry of Health has developed a strategy in rare diseases for the National Health system with the implication of central and local stakeholders and also patient advocacy groups. The strategy includes the need of developing registries of patients, prevention campaigns and early diagnostic [36].

The limited availability of economic evaluations of these drugs [37,38] is one of the limitations of the present study. In addition, the assessments provided by the NICE and the SMC reports are not transparent regarding the determination of the ICER [9], making it difficult to perform comparisons and draw conclusions. What the reports do highlight is the importance of these types of agreements for favouring patient access to these therapies. Another issue to consider is that drug prices in England and Scotland are not necessarily comparable to those in Spain, which limits extrapolation of the results. Even so, both the NICE and the SMC evaluations are good guides and references and permit the conclusion that in general, orphan drugs have ICERs well above the widely considered efficiency thresholds and this circumstance is likely to be present in other countries.

The results from this study highlight the need for establishing mechanisms to speed the approval of orphan drugs and to reduce the variability in the approval by enhancing the transparency of price and reimbursement decisions.

Conclusion

Although there have been legislative measures that promote the development of therapies for rare diseases, these therapies account for 31.2% of commercialization in Spain, with time intervals from national authorization to commercialization that, on average, exceed a year and a half. This lag has a great impact on the expectations of patients who are delayed from being able to benefit from therapies for diseases for which there are often no alternatives available.

The scientific evidence generated for each orphan drug that has EC approval is sound and of high quality, including mostly phase III, randomized, double-blind and open-label clinical trials, although in many cases, the numbers of patients in the clinical trials are limited. An inverse correlation is observed between the number of patients affected and the monthly pharmacological cost per patient for these drugs.

The ICERs in the analysed reports show a great deal of variability, with 63% of the assessments being above the recognised thresholds and with a mean value exceeding £100,000/QALY.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; at the time of the study, JAS and TD were employees of Eli Lilly and hold Eli Lilly shares; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

MN, BG, JAS and TD designed the study, developed the methodology and wrote the manuscript. MN and BG collected the data and performed the analysis.

Authors' information:

At the time this work was developed, MN and BG were students at University Carlos III, Madrid (UCIIIM). JAS and TD are invited professors at Universidad Carlos III de Madrid (UCIIIM).

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