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PSY137: Orphan drugs to treat rare diseases: the Italian way for an early access

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Introduction

A major challenge for Regulatory Agencies is to achieve a balance between the need of a rapid access to new therapies for patients and the assessment of the benefit-risk ratio. Italian Law 648/96 (published on the Italian Official Journal (GURI) n.300 – Dec, 23rd 1996) ensures an early access on the market for unauthorized drugs until the regular approval iter completion. The Law allows, on the costs of the National Health Service, the use of three types of medical products: innovative drugs for which the sale is authorized abroad, but not in Italy; drugs which have not yet received an authorization, but have undergone clinical trials; and drugs to be used for a different therapeutic indication from that one which has been authorized (off-label use). The original art. 1, sub. 4, Law 648/96 allows the prescription of these drugs (on the cost of NHS), provided that phase II or III clinical trials with favourable evaluation in terms of efficacy and safety were published, but only if any other therapeutic alternative isn't available. It was a exception to Legislative Decree 178/91, art. 2, sub 2: subsequently amended by the Legislative Decree 219/06, art. 6, sub 1 "no medicinal product can be put on the market without the AIFA (Italian Medicines Agency) authorization (AIC). As per regulation the authorization could be obtained by national procedure, mutual recognition or decentralized procedures or using the EU authorization, through the centralized procedure, that grants, in accordance with the EMEA Regulation, the authorization throughout each European countries. Moreover, the centralized procedure is mandatory for medicines designated as orphan drugs.
By the amendment published on May 2014 (Law 79/2014, art. 4bis), the Technical and Scientific Committee (CTS) of AIFA can include a medicine in the official 648/96 list, even if there's a therapeutic choice, but the economic advantage is assured. According to 648/96 Law, healthcare operators or patients' associations could request the early access for drugs, submitting a formal request to AIFA, listing the efficacy's evidence, inferable from scientific literature. After evaluation by AIFA, the use of the drug is approved for clinical use, if deemed appropriate. The medicine becomes available to patients, with inclusion and exclusion criteria set by AIFA. However the medicine is subjected to surveillance programs, with which data the 648/96 list is periodically updated.

Objective

This study is aimed to assess how many drugs, designated as orphan drug by EMA, entered in the Italian market trough the 648/96 law, analyzing their specific indications and characteristics and evaluating the impact of this early access tool on the time to patient.

Methods

The analysis considers all the medicines for which EMA's Committee for Orphan Medicinal Products (COMP) granted the orphan designation status from the beginning on (Regulation (EC) No 141/2000). By analyzing the 648/96 Law drugs' list, we selected the orphan drugs authorized within the law, for the specific indication (rare condition). For each one of these drugs we also checked the official publications into the Italian GURI, in order to collect all the information about the conditions granted by AIFA for their approval (i.e. MEAs -Managed Entry Agreements-) application, duration of their permanence into the 648 List). When applicable we also analized the Monitoring Registry. Lastly we checked the date of AIFA pricing and reimbursement decree and, at Regional level, the date of the first purchase of the product into each one of the 21 Italian Regions. In Italy, indeed, once the National phase is completed, the drug approval process needs to undergo further steps that may be quite different from a Region to the other, with, consequently, a different time to patient, depending on the existence of a local formulary or further evaluation steps.

Figure 1: Italian regional formularies status

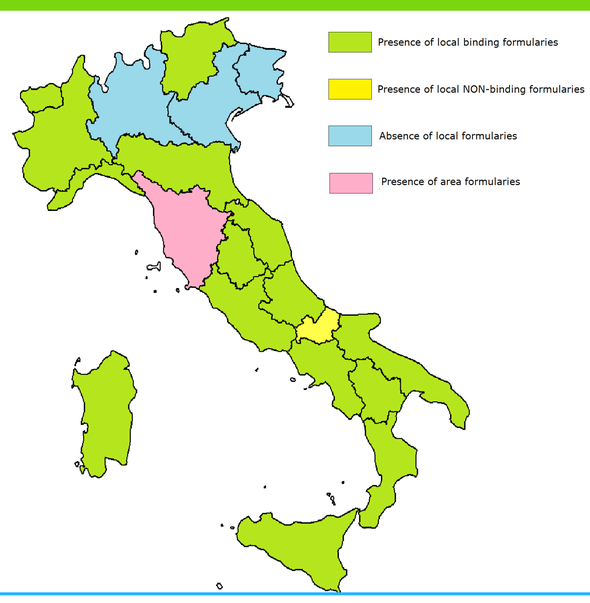


Table 1: List of products designated as Orphan drug, approved within the Italian 648/96 Law

Product	Active substance	Disease	Date ODD	648 vs CHMP (days)	648 vs AIFA P&R GURI (days)
Adcetris	brentuximab vedotin	Hodgkin lymphoma	14/01/2009	104	-600
Ceplene	histamine dihydrochloride	Acute myeloid leukaemia	11/04/2005	938	-299
Defitelio	defibrotide	Hepatic veno-occlusive disease	29/07/2004	222	-440
Elaprase	iduronate-2-sulfatase	Mucopolysaccharidosis, type II (Hunter Syndrome)	11/12/2001	-123	-1.742
Firdapse	3,4 diaminopyridine phosphate	Lambert-Eaton myasthenic syndrome	18/12/2002	205	-621
Iclusig	ponatinib	Acute lymphoblastic leukaemia, chronic myeloid leukaemia	02/02/2010	184	-445
Ketoconazole HRA	ketoconazole	Cushing's syndrome	23/04/2012	-133	-687
Lysodren	mitotane	Adrenal cortical carcinoma	12/06/2002	-2.237	-2.638
Mozobil	plerixafor	Mobilize progenitor cells prior to stem cell transplantation	20/10/2004	119	-790
Naglazyme	galsulfase	Mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy syndrome	14/02/2001	53	-474
Obizur	susoctocog alfa	Haemophilia A	20/09/2010	22	-553
Plenadren	hydrocortisone (modified-release tablet)	Adrenal insufficiency	22/05/2006	302	-589
Scenesse	afamelanotide	Erythropoietic protoporphyria	08/05/2008	-1.622	-2.299
Signifor	pasireotide	Cushing's disease, acromegaly	08/10/2009	233	-737
Soliris	eculizumab	Paroxysmal nocturnal haemoglobinuria	17/10/2003	32	-437
Trisenox	arsenic trioxide	Acute promyelocytic leukaemia	18/10/2000	-930	-
Vidaza	azacitidine	Myelodysplastic syndromes	06/02/2002	173	-567
Vimizim	elosulfase alfa	Mucopolysaccharidosis, type IVA (Morquio A syndrome)	24/07/2009	127	-403
Vyndaqel	tafamidis	Familial amyloid polyneuropathy	28/08/2006	-180	-835
Xagrid	anagrelide hydrochloride	Essential thrombocythaemia	29/12/2000	-205	-

(*) Product name, active substance, disease or condition referred to the OD, days between 648/96 and CHMP approval (referred to the specific indication), days between 648/96 and AIFA Price and Reimbursement (P&R) decree published (GURI)

Figure 2: Orphan drugs evolving trend in Italy, considering the time to patient

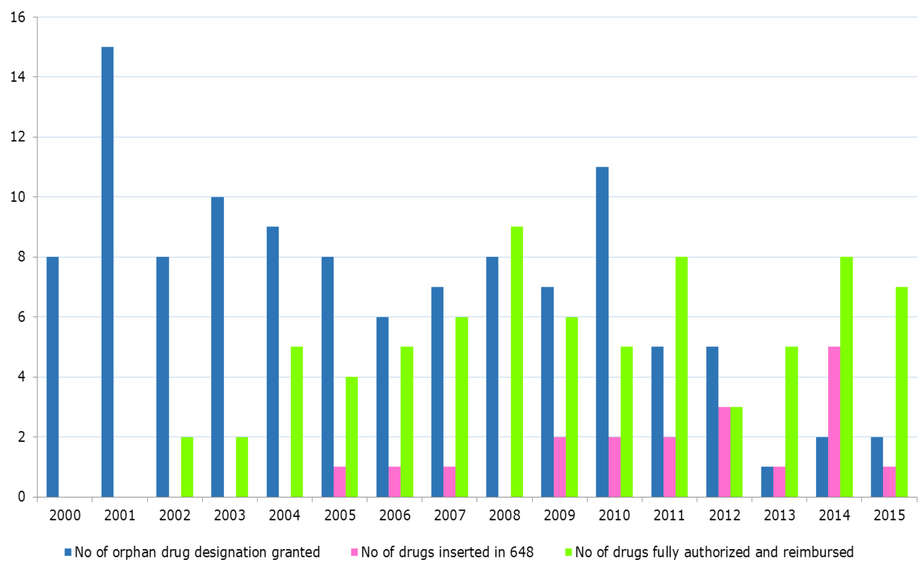
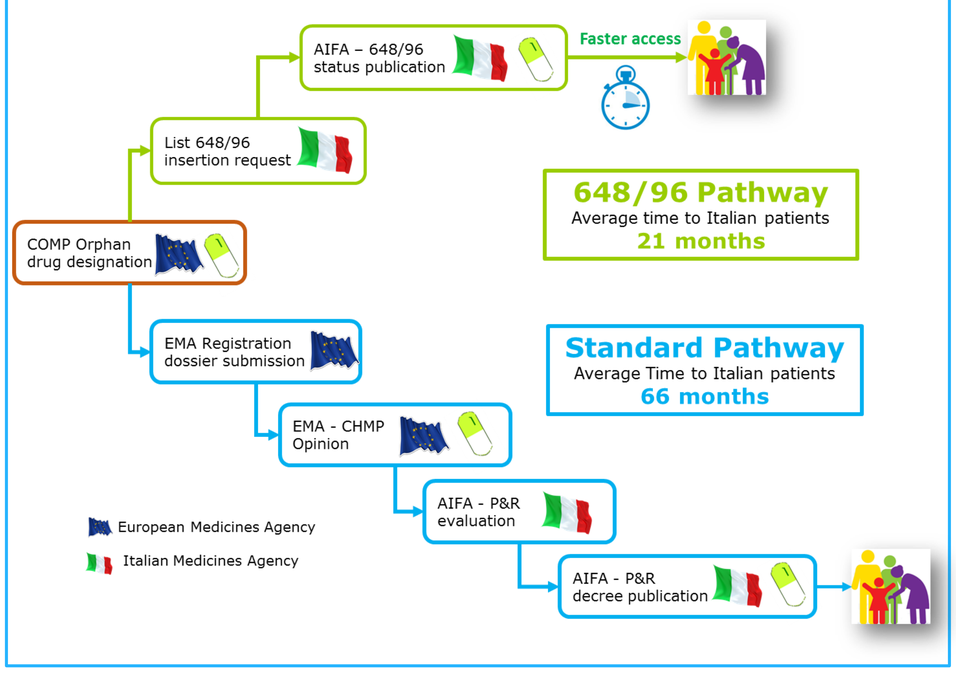


Figure 3: Italian patient access pathway



Results

From 2000 on, the EMA's COMP granted Orphan Designation (OD) to 112 medicines, further authorized by CHMP (Committee for Medicinal Products for Human Use). Twenty of 112 (18%) have been insert into the Italian 648/96 list; haematology/onco-haematology is the therapeutic area most interested in it (8/20; 44%), followed by metabolic and autoimmune diseases. To date, 18 of 20 drugs completed the full Italian price and reimbursement process and the remaining two drugs/indications are still authorized trough 648/96, waiting for the National full approval.

By analyzing our data, the mean time spared, starting from CHMP approval, thanks to 648/96, is 136 days (around 5 months). Considering the mean time spared starting from the 648/96 to AIFA pricing and reimbursement process completion (Decree publication into the GURI) is 842 days (around 28 months).
The most powerful data are related to the final timing needed to patient: since the orphan designation is obtained, a drug involved in the 648/96 Pathway, reach the patient in 21months (versus the Standard Pathway, in 66 months).

Out of the 20 orphan drugs authorized under 648/96, 9 have been reimbursed with a Monitoring Registry, and it seems to be associated with a mean shortening of the timing of approval. This is very interesting considering the growing importance recognized to the regulatory use of real world data, a key requirement of evidence of clinical effectiveness and cost-effectiveness for market access. Some of these Registries (5/9) have been associated with a cost sharing or with a risk sharing (payment by results) managed entry agreements. The others (4/9) are registries intended to define and control the appropriateness of use.

Focusing on Regional Access, considering that our database are recording the date of the first purchase in each of the Italian Region starting from January 2013, our data are referred to 7/20, products classified in the 648/96 list, and 22/92 products, not inserted into 648/96 list. By analyzing these data, it is interesting to note that the average time from the GURI publication (of the 648/96, or P&R decree) to the first regional purchase is significatively lower for products classified in 648/96 list (38 days) than all the other medicines (227 days).
These data are very interesting, considering the specific characteristics set by the EMA for an orphan drug: it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Conclusions

About 30 million people living in Europe and around 2,5 million of Italians suffer from a rare disease; therefore the development and authorization of medicines for rare disease is a key issue. Together with EMA, AIFA developed some regulatory tools, to accelerate the time to patients.

The current analysis shows that the 648/96 law is an useful and efficacious tool to provide physicians, with a timely and demonstrative experience, a new drug, pending the EMA approval or local registration, and patients with an early access to new safe and efficacious therapeutic options.

Thanks to Law 648/96, on average, Italian patients were able to save 45 months (around 4 years), with the opportunity to be treated with the newest and innovative cures for their rare disease.

The analysis shows the important role of the Italian structured and complex healthcare system that, thanks to its dedicate legislation and to specifically designed tools (i.e. Monitoring Registries and MEAs), allows to obtain a faster access to patients and the appropriateness of use. This process ensures to the NHS an expenditure control, granting, at the same time, the use of the right and most innovative drug for the right patient.

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