PRO76: Italian 648/96 Law application between Jan 2013 and September 2019: focus on orphan drugs

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Introduction

In Italy, access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments. The centralized procedure represents the standard access route; whenever an orphan drug has no marketing authorization, patient access is ensured through different early access schemes. One of these early access tools is the Law 648/96.

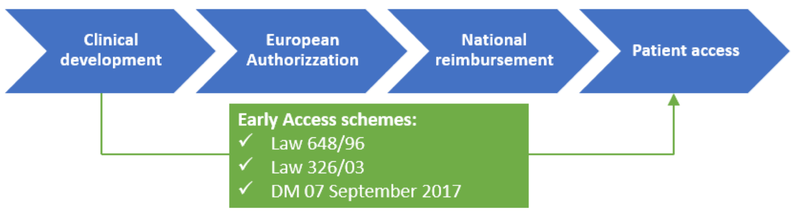

***Figure 1* – Drug's Patient access flow with and without early access schemes**

The Law 648/96 allows the supply of certain medicines reimbursed by the NHS, in order to respond to pathological conditions for which no alternative therapeutic option is available. In order to include a medicine into the lists implemented by the Law 648/96 (the so-called 648 List), one of the following conditions shall be met:

- ✓ innovative medicines holding a marketing authorization granted in any European country, but not in Italy;
- ✓ medicinal products not yet authorized, but undergoing clinical trials;
- ✓ Medicinal products to be used for a therapeutic indication different from the one that had been authorized in Italy

In all these cases it is necessary to have results of Phase II study, which show an adequate efficacy/risk ratio to support the use in the requested indication.

When therapeutic alternatives are available, the medicinal product to be used for a therapeutic indication different from the authorized one (off-label use) can still be included in the 648 List, provided that this use is recognized by the medical-scientific community, subject to parameters of affordability and appropriateness.

The inclusion of a medicinal product in the 648 List is performed by AIFA on the basis of a documented request from patients' associations, scientific societies, health facilities, universities or following recommendations of AIFA's Scientific-Technical Committee (CTS). The list of orphan drugs (ODs) included in the Law 648/96 can be downloaded from AIFA's website (https://www.aifa.gov.it/legge-648-96)

Objective

This study aimed to assess AIFA's approach on the inclusion request of ODs to the 648 List.
Approvals, rejections and methods followed by AIFA for its decisions were reviewed.

The permanence time in 648 List and the time market of orphan drugs were analyzed, when applicable.

Methods

The drugs' panel was built by systematically reviewing the CTS meetings decision (office "Area pre-autorizzazione") from January 2013 to September 2019, checking the number and characteristics of ODs evaluated for the inclusion in the 648 List, and analysing each single decision taken by the CTS.

For all of them, we systematically checked the issuing date of the marketing authorisation valid throughout the European Union, the date of inclusion in the 648 List, the date of exclusion from the 648 List, the date of the price publication in the Italian Official Journal (I.O.J.), the launch date in the reimbursed class.

The related dates of reimbursement were collected via the official websites of: Agenzia Italiana del Farmaco (AIFA), The European Medicines Agency (EMA), I.O.J., Community Register of Medicinal Product, FARMADATI.

The differences between the time of EU approval and the inclusion in the 648 List, the permanence time in the 648 List, and, where applicable, the time to market have been evaluated (mean and median).

Results

AIFA evaluated 45 requests for orphan drugs's inclusion in the 648 List during the considered time-frame of this analysis:

- ✓ 13 requests were approved (29%);
- ✓ 32 requests were not approved (71%).

There were several requests for same drugs and for this reason the total number of the evauated drugs was equal to 37.

Active substance (drug name)	Date of Orphan Designation	Indication for the inclusion request in the 648 List
Anagrelide (Xagrid)	30/12/2000 No more Orphan Designation: November 2016	Treatment of Essential Thrombocythemia first line in young patients (< 40 years)
Ataluren (Translarna)	27/05/2005	Treatment of Duchenne muscular dystrophy due to nonsense mutation in the dystrophin gene, in patients ≥ 5 years old
Bosentan (Tracleer)	15/02/2001 I indication 18/03/2003 II indication No more Orphan Designation: I indication May 2012 (expired); II indication April 2014 (withdrowal)	Chronic thromboembolic pulmonary hypertension CTEPH for patients not eligible to treatment with Pulmonary endarterectomy (PEA) or with recurrence of pulmonary hypertension after intervention
Chetoconazolo (Ketoconazole HRA)	23/04/2012	Treatment of Cushing syndrome
Cisteamina cloridrato (Cystadrops)	07/11/2008	Prevention and removal of corneal cystine crystal deposits in nephropathic cystinosis
Cladribina (2-clorodeossiadenosina) (Litak)	18/09/2001 No more Orphan Designation: April 2014	Aggressive systemic mastocytosis as first line therapy; mast cell leukemia and first line therapy or a subsequent line
Defribrotide (Defitelio)	29/07/2004	Severe hepatic veno-occlusive disease (VOD) after transplant of haematopoietic stem cells
Dinutuximab beta (Qarziba)	08/11/2012	Neuroblastoma at high risk in patients of at least 12 months of age after previous induction chemotherapy with at least a partial response, followed by myeloablative therapy and a stem cell transplantation. Relapsing or refractory neuroblastoma, with or without residual disease. In patients with relapsing/refractory disease and in patients who have not achieved a complete response after first-line therapy, Dinutuximab beta Apeiron should be associated with interleukin-2 (IL-2) therapy.
Eculizumab (Soliris)	17/10/2003 24/07/2009 29/07/2014	Prevention of recurrences from Atypical haemolytic uremic syndrome (aHUS)
Edaravone	19/06/2015 No European Marketing Authorization	Treatment of amyotrophic lateral sclerosis; Treatment of patients with a definite or probable diagnosis of amyotrophic lateral sclerosis
Idrocortisone(Plenadren)	22/05/2006	Treatment of West syndrome
Plerixafor (Mozobil)	20/10/2004	Use in donors (family or registry) for allogeneic stem cells transplantation
Pomalidomide (Imnovid)	08/10/2009	Treatment of Amyloid light-chain (AL) amyloidosis

Table 1 – ODs included in the 648 List

11/13 (~85%) ODs inserted in the 648 List are still present there.
Only two (~15%) ODs were excluded from the 648 List. The reason for the exclusion, in both cases, was due to obtaining the reimbursement status from AIFA for the therapeutic indication specified in the 648 List.
The median permanence time in the 648 List for these two drugs was 588,5 days.

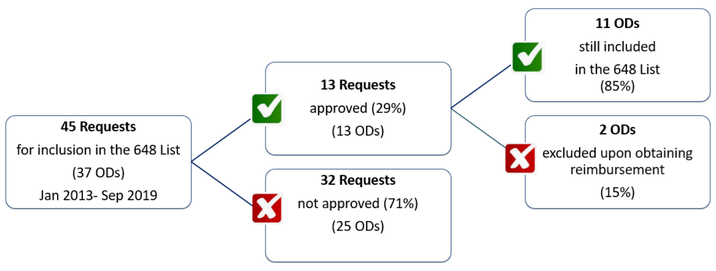

Figure 2 – Design of the study

These drugs were made available for Italian patient in average in 82 days (median 137; range -442 to 763) after the European Marketing Authorization.

The Anatomical Therapeutic Chemical (ATC) code mainly represented was the L (antineoplastic and immunomodulant agents) (50%).

The other ATCs were the following: M - Musculoskeletal system, C - Cardiovascular system, J - Anti-infectives for systemic use, S - Sensory organs, B - Blood and blood forming organs, H - Systemic hormonal preparations, excl. sex hormones and insulins. They were equally represented (8% for each).

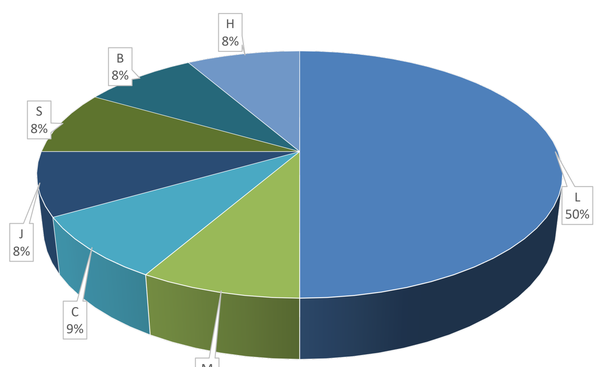

***Figure 3* – Positive evaluation by ATC code**

Negative opinion was given to 32 requests and the reasons were as follows:

- ✓ 24/32 (75%): not specified;
- ✓ 5/32 (15,6%): the access to Fondo AIFA 5% (326/2003 Law) was suggested;
- ✓ 1/32 (~ 3%): the inclusion in the Law 94/98 (Legge Di Bella) was suggested;
- ✓ 1/32 (~ 3%): due to the presence of the valid treatment option on the market;
- ✓ 1/32 (~ 3%): due to the lack of scientific data.

On average there were 2 CTS evaluations per each request that received a negative opinion.

Active substance (Drug)	No. of CTS evaluations	Reason for a negative opinion
Acido colico (Orphacol)	1	Fondo AIFA 5%
Asfotase alfa (Strensiq)	2	Fondo AIFA 5%
Ataluren (Translarna)	1	Not specified
Blinatumomab (Blincyto)	1	Not specified
Cabozantinib (Cometriq)	3	Analogous produc on the market
Caplacizumab (Cablivi)	3	Not specified
Cerliponase alfa (Brineura)	1	Not specified
Daunorubicina + citarabina (Vyxeos)	1	Not specified
Eliglustat (Cerdelga)	2	Not specified
Elosulfase alfa (N-acetilgalattosammina-6-solfatasi ricombinante umana, rhGALNS) Vimizim	3	Lack of scientifc evidence
Emoderivato plasminogeno	1	Not specified
Ibrutinib (Imbruvica)	1	Not specified
Icatibant (Firazyr)	1	Not specified
Idebenone (Raxone)	1	Not specified
Idebenone (Raxone)	1	Not specified
Idebenone (Raxone)	1	Not specified
Idebenone (Raxone)	1	Not specified
Ivacaftor (Kalydeco)	4	Fondo AIFA 5%
Metreleptina (Myalepta)	1	Not specified
Migalastat (Galafold)	1	Fondo AIFA 5%
Olaparib (Lynparza)	1	Not specified
Olaparib (Lynparza)	3	Not specified
Pomalidomide (Imnovid)	4	Not specified
Pomalidomide (Imnovid)	1	Not specified
radiofarmaco 177Lu-Dotatate (Lutathera)	3	Not specified
radiofarmaco 177Lu-Dotatate (Lutathera)	2	Not specified
Riociguat (Adempas)	1	Not specified
Sapropterina dicloridrato (Kuvan)	1	Di Bella Law
Sebelipase alfa (Kanuma)	1	Fondo AIFA 5%
Thalidomide (Thalidomide Celgene (previously Thalidomide Pharmion)	1	Not specified
trabectedina (Yondelis)	1	Not specified
Linfociti T allogenici geneticamente modificati con un vettore retrovirale codificante per una forma troncata del recettore umano a bassa affinità del fattore di crescita nervoso (ΔLNGFR) e la timidina chinasi del virus herpes simplex I (HSV-TK Mut2) (Zalmoxis)	2	Not specified

Table2 – ODs not included in the 648 List

Conclusions

The Law 648/96 is one of the early access schemes in Italy, which allows the supply of specific drugs - not yet available in Italy or undergoing clinical trials or used off-label – that are reimbursed by the NHS. These drugs are inserted in the so-called 648 List and supplied to patients in order to respond to pathological conditions with no alternative therapeutic options (when therapeutic alternatives are available the drug's inclusion in the 648 List is subject to parameters of affordability and appropriateness and its use in the considered indication, different from the authorized one, shall be recognized by the medical-scientific community).

Between Jan 2013 and September 2019, 45 requests on inclusion in the 648 List (i.e. 37 ODs) were evaluated and 29% of them were approved. Of these, 11/13 drugs (85%) are still in the 648 List and only 2/13 (15%) were excluded after obtaining reimbursement status for the 648 indication (588,5 days median time). The most frequent ATC was the L (antineoplastic and immunomodulant agents) (50%).

Our data showed that the 648 List is a powerful early access tool to allow early access to ODs for Italian patients.

REFERENCES:

AIFA-CTS: https://www.aifa.gov.it/archivio?strutture=96918
648/96 Law: https://www.aifa.gov.it/legge-648-96
Italian Official Journal: https://www.gazzettaufficiale.it/

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