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Italian 648/96 law application between Jan 2013 and Dec 2015: focus on orphan drugs

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Introduction

The Italian Law 648/96 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 therapeutic indication different from the one which had been authorized (off-label). The original art. 1, sub. 4, Law 648/1996 allowed the prescription (paid by the producer) of these drugs, provided that phase II or III clinical trials with favourable evaluation in terms of efficacy and safety were published, but only if no any other therapeutic alternative is available. The following derogation to Legislative Decree 219/06, art. 6, sub 1, stated that: "no medicinal product can be put on the market without either an AIFA authorization (Autorizzazione all'Immissione in Commercio - AIC), which may be national, by mutual recognition or by decentralized procedures or an EU authorization granted in accordance with the EMEA Regulation".

By the amendment published on May 2014 (law 79/2014, art. 4bis), the Technical Committee of AIFA can include a given medication in the official list even if there is a therapeutic choice. This is an important change: by this new law, AIFA can grant an authorization for a new indication, based only on scientific evidences, granting to Italian patients the access to innovative drugs.

According to 648/96 Law, health operators or patients associations can request early access to medications by submitting a written request to AIFA, underlying the evidence of efficacy as reported in the scientific literature. The request is discussed by the Technical and Scientific Commission (CTS) of AIFA and approved for clinical use if deemed appropriate. Thus, the medication becomes available to patients with inclusion and exclusion criteria set by AIFA. In addition, the medication is subject to a program of surveillance and should be reported in a list which is periodically updated.

Objectives

This study aimed to assess AIFA's approach, by reviewing approvals, rejections and methods followed by AIFA for its decisions, and to analyse their temporal evolution, with a specific focus on orphan drugs.

Methods

In order to ensure transparency in the decision process, AIFA makes electronic files available through an online system of transparency. The most important information are published online, after each AIFA CTS meeting. By connecting to the dedicated page, we systematically performed a review of each single document (Verbali CTS - "Esiti Ufficio Ricerca e Sperimentazioni Cliniche"), and collected all the available information.

Reports of CTS meetings from January 2013 to December 2015 were reviewed, checking number and characteristics of drugs under evaluation, and analyzing each single decision taken by CTS.

In order to deepen the analysis, we also checked all the Determine and Gazzette Ufficiali related to 648 Law, published in the considered timeframe. As an example, in 2013 and 2014 some specific 648 lists have been published, containing all the 648-approved products for Neurology (4), Transplantation (5), Antivirals (7) or Cardiology (8). All these information are public and available on a dedicated section of the official AIFA site (http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinic).

To complete our analysis, we checked the actual regulatory status of each product reviewed by AIFA, through the "Patient Access Monitor" Portal, a new informative system, which collects all the public information about drugs. It collects their approval history, from the first European approval, along all the modifications (i.e. indications, prices, dosages, variations) and the relevant National steps, until the actual availability for the patients at local level. This new platform allows to have an integrated access to all the information available on official and institutional sources (such as EMA, AIFA, Gazzetta Ufficiale, etc.), ensuring a complete overview.

Table 1: List of all the the orphan drugs evaluated for the inclusion in 648 lists (Jan 2013-Dec 2015)

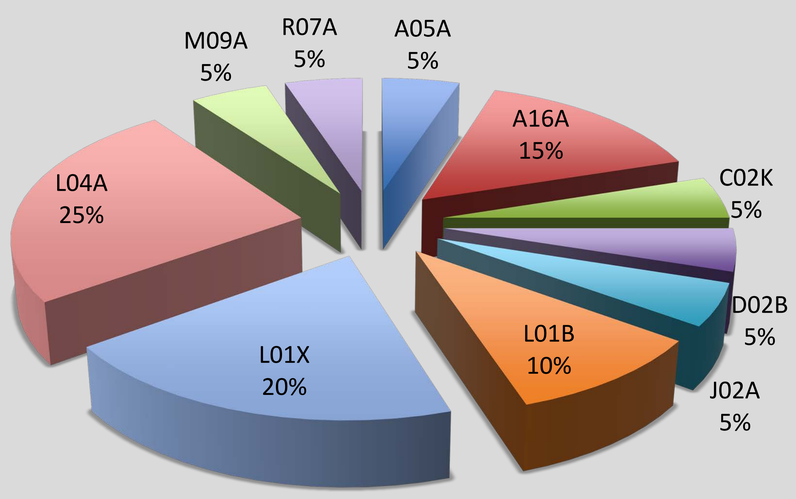
CTS Meeting(s)	648 Indication	CTS Decision	Active substance	Brand name	Orphan Designation (OD)	OD Date	Official registration	Legislative reference
July 2015	Chronic Thromboembolic Pulmonary Hypertension (CTEPH)	Negative	riociguat	Adempas	Treatment of pulmonary arterial hypertension	19/12/2007	YES	GU 28/2/2015 n. 49
July 2013, October 2014, December 2015	Duchenne muscular dystrophy (DMD)	Positive	ataluren	Translarna	Treatment of Duchenne muscular dystrophy	27/05/2005	NO	GU 17/12/14 n. 292; GU 31/12/2015 n. 303; GU 07/01/16 n. 4
October 2014, May 2015	Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)	Negative	canakinumab	Ilaris	Treatment of tumour-necrosis-factor-receptor-associated periodic syndrome	08/11/12	YES (but not for this indication)	GU 29/12/2014 n. 300; GU 25/5/2015 n. 119
October 2013, February 2014, April 2014	Medullary thyroid cancer (MTC)	Negative	cabozantinib	Cometriq	Treatment of medullary thyroid carcinoma	05/02/09	NO	P&R process ongoing
April 2013; January 2014	Acute Myeloid Leukemia (AML)	Negative	clofarabina	Evoltra	Treatment of acute lymphoblastic leukaemia	05/02/2002	YES (but not for this indication)	GU 21/03/2007 n. 67
May 2015	Mantel Cell Lymphoma (MCL)	Negative	ibrutinib	Imbruvica	Treatment of mantle-cell lymphoma	12/03/2013	YES	GU 21/12/2015 n. 296
April, September and October 2013 and March 2014	Cystic fibrosis (CF)	Negative	ivacaftor	Kalydeco	Treatment of cystic fibrosis	08/07/2008	YES	GU 4/5/2015 n. 101
October 2015	Lysosomal Acid Lipase Deficiency (LAL-D)	Negative	sebelipase alfa	Kanuma	Treatment of lysosomal acid lipase deficiency	17/12/2010	NO	P&R process ongoing
Decembre 2013	Phenylketonuria (PKU) in children less than 4 years	Negative	sapropterina dicloridrato	Kuvan	Treatment of hyperphenylalaninaemia	08/06/04	YES (but not for this indication)	GU 8/7/2009 n. 104
July 2015	Langerhans cell histiocytosis (LCH)	Positive	cladribin	Litak	Treatment of mastocytosis	05/08/2013	YES (but not for this indication)	GU 19/8/2013 n. 193
July and December 2014, February 2015	Advanced ovarian cancer	Negative	olaparib	Lynparza	Treatment of ovarian cancer	06/12/07	NO	P&R process ongoing
October 2014	Inborn errors in primary bile acid synthesis	Negative	cholic acid	Orphacol	Treatment of inborn errors of primary-bile-acid synthesis	17/12/02	NO	P&R process ongoing
July 2013	Multiple Myeloma (MM)	Negative	pomalidomide	Imnovid	Treatment of multiple myeloma	08/01/2009	YES	GU 5/08/2015 n. 180
April 2014, March and July 2015	Erythropoietic protoporphyria (EPP)	Positive	afamelanotide	Scenesse	Treatment of erythropoietic protoporphyria	08/05/08	NO	GU 6/5/2014 n.103; GU 29/04/2015 n. 98; GU 8/8/2015 n. 183
December 2014	Atypical hemolytic uremic syndrome (SEUa; relapse prevention)	Positive	eculizumab	Soliris	Treatment of atypical haemolytic uraemic syndrome (aHUS)	24/07/09	YES (but not for this indication)	GU 5/2/2015 n. 29
September and October 2013 and April 2014	Mucopolysaccharidosis type IVA	Positive	elosulfase alfa	Vimizim	Treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome)	24/07/2009	YES	GU 27/06/14 n. 147
March 2013, January 2014	Essential thrombocythemia	Positive	anagrelide	Xagrid	Treatment of essential thrombocythaemia	29/12/2000	YES (but not for this indication)	GU 04/03/14 n. 52
March 2014	Cushing's syndrome	Positive	ketoconazole	NA	Treatment of Cushing's syndrome	23/04/12	NO	GU 15/05/14 n. 111

Table 2: Time between EU and "648" approval

Active substance	Brand name	OD Designation	EU Marketing Authotization	648 approval
ataluren	Translarna	Treatment of Duchenne muscular dystrophy	31/07/14	17/12/14
cladribin	Litak	Treatment of mastocytosis	14/04/04	19/08/13
afamelanotide	Scenesse	Treatment of erythropoietic protoporphyria	22/12/14	06/05/14
eculizumab	Soliris	Treatment of atypical haemolytic uraemic syndrome (aHUS)	20/06/07	05/02/15
elosulfase alfa	Vimizim	Treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome)	18/04/14	27/06/14
anagrelide	Xagrid	Treatment of essential thrombocythaemia	16/11/04	04/03/14
ketoconazole	NA	Treatment of Cushing's syndrome	19/11/14	15/05/14

Out of 7 orphan drugs included in 648 List during the timeframe 2013-2015, four are drugs recently approved by EMA (2014): ataluren, afamelanotide, elosulfase alfa and ketoconazole. For two of them the inclusion in 648 List preceded also the EU approval: afamelanotide has been included in 648 on May 2010 for the first time (GU 15/5/2010 n. 112), based on the total absence of therapeutic alternatives and a similar decision has adopted for ketaconazole (GU 15/5/14 n. 111). Ataluren and elosulfase alfa have been made available for Italian patients through 648 List just 5 and 2 months after the European approval. For drugs approved previously by EMA (cladribin, eculizumab and anagrelide), the inclusion into the 648 list affected indications different from the initially approved.

Figure 1: "648 approved" orphan drugs distribution for ATC-4 code



The main represented ATC-4 for products under AIFA's evaluation were: L04A (immunosuppressant) 25%, L01X (other antineoplastic agents) 20% and A16A (other alimentary tract and metabolism products) 15%.

Results

Out of 18 examined applications, 7 received a positive evaluation and 11 a negative evaluation: 4/11 because of lackness of scientific data; 2/11 because officially approved in the meantime and 1/11 in presence of valid therapeutic alternatives. For the missing 4/11, CTS suggested to access Law 326/2003 Fondo AIFA 5% (a special fund for the reimbursement of orphan and life saving drugs awaiting market entry) and to the Law 94/98 Legge Di Bella (which allows doctors to use, under particular circumstances, drugs in a compassionate way for patients with rare diseases for which there is no established therapy). In the timeframe under analysis, 4 drugs obtained a full registration and completed their price and reimbursement process and other four are at this time (May 2016) under negotiation with AIFA (caboantinib, cholic acid, olaparib and sebelipase alfa).
Out of the 7 approved orphan drugs included in 648 List (Jan 2013-Dec 2015), just one, eculizumab, is a drug under monitoring for 648 indication through the system of AIFA Registries.

As shown in AIFA Osmed Report 2014, between 2013 and 2015 some more orphan drugs have been included in 648 List: bosentan (Tracleer, GU 28/2/2013 n. 50, whose two orphan designations were respectively withdrawn and expired), defibrotide (Deftelio, GU 4/3/2014, which has been excluded with GU 28/5/15 n. 122 because of the registration process closure) and hydrocortison for the treatment of West Syndrome (GU 5/12/2013 n. 285).

Conclusions

Law 648/96 allows a cohort of patients access to drugs demostrating clear benefit but being still under clinical investigation, including drugs that have obtained a marketing authorization abroad but are not yet marketable in Italy. Therefore, the Italian 648/96 Law is an useful tool to provide physicians with a timely and demonstrative experience of a new drug, pending the EMA approval or local registration, and patients with an early access to new safe and efficacious therapeutic options.

Together with Fondo AIFA 5% and Law 94/98, Law 648/96 reflects the strong AIFA's commitment to allow early access to orphan drugs for Italian patients.

References

- Law 648/96
- Legislative Decree 219/06
- Law 79/2014, art 4bis
- http://www.agenziafarmaco.gov.it/it/commissioni
- http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinica
- "Patient Access Monitor" Portal
- Ministerial Decree 8 May 2003
- Law 94/1998 and Law 326/2003 (Fondo AIFA 5%)
- http://www.whocc.no/atc_ddd_index/
- AIFA, Rapporto Osmed 2014

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