ITALIAN LAW 326/2003 FOR THE REIMBURSEMENT OF ORPHAN AND LIFE SAVING DRUGS AWAITING MARKET ENTRY: APPROVALS, REJECTIONS AND METHODS IN AIFA'S EVALUATION PROCESS BETWEEN JANUARY 2013 AND OCTOBER 2015

Authors: Prada M[1], Bertozzi C[1], Proietti B[1], Urbinati D[2]

[1]Intexo, Roma, Italy; [2]IMS Health, Milano, Italy

Introduction

Article 48 of Law 326/2003 requires all drugs companies operating in Italy to pay 5% of their promotional expenses to an independent research fund (Fondo AIFA 5%). This fund is designed to promote orphan diseases research and to make available to rare diseases' patients medicines awaiting market entry.

Therefore, according to the law, half of the fund should be devoted to providing access to medicines for rare diseases before market authorization, and the other half should be devoted to promote independent research and related activities.

Thanks to the annual reports performed by the AIFA's Italian National Observatory on Drugs Utilization (OSMED), we acknowledge that in 2013 and 2014 the expenses for patients who acceded the Fondo were 138.382 Euro and 239.895 Euro respectively (more details available in Table 2). Data related to 2015 will be available in mid 2016.

Reference centers or hospitals are in charge of each application, for which they are expected to provide a short clinical report, with the definition of therapeutic plan, dosages and cycles number.

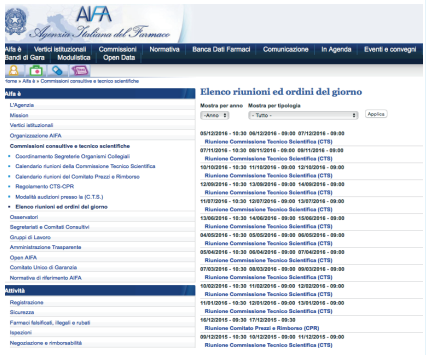
Objectives

This study is aimed to assess how many applications have been submitted to the Technical Committee of AIFA (CTS) and how they have been evaluated.

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 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 collecteding all the available information.



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

To complete our analysis, we also 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.

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Table 1: list of all the reviewed drugs (Jan 2013-Oct 2015)

Active substance under evaluation	Approved requests (pts)	Last request	On the Italian Market	Registration details	Reimbursement Class
abiraterone	3/3	mar-13	YES	Det AIFA 7/3/2013 (metastatic prostate carcinoma castration resistant during or after CT) and new indication 4/09/2014 (pre-chemotherapy)	H
acido colico	0/2 (compassionate use program active)	mar-15	NO	European Marketing Authorization 12/09/2013 (EMEA/H/C/001250)	n.a.
ataluren	0/1 (waiting for EMA's decision)	dec 13	NO	European Marketing Authorization 31/07/2014 (EMEA/H/C/002720)	n.a.
blinatumomas	0/1 (compassionate use program active)	mar-15	NO	Positive opinion CHMP 24/09/2015	n.a.
brentuximab vedotin	0/6 (M.D. 8/5/2003)	jul 13	YES	Det AIFA 12/06/2014 (Hodgkin Disease and anaplastic large cell lymphoma)	H
carfilzomib	1/1	jan 15	NO	Positive opinion CHMP 24/09/2015	n.a.
delamanid	1/1	oct 14	NO	Det AIFA 17/07/2015 Classification in C(nn); European Marketing Authorization 28/04/2014	n.a.
glucarpidase	0/1 (no conditions to access the Fondo)	jan 14	NO	Whitdrawn application (EMA) 21/05/2007	n.a.
ibrutinib	0/2 (waiting the drug to be available in the USA; in the meantime suggestion to ask it to the Company through DM 8/5/2003)	may 14	NO	Det AIFA 26/01/2015 Classification in C(nn)	n.a.
ivacaftor	4/31 (then CTS suggested to apply the compassionate use program activated by the Company)	mar-15	YES	Det AIFA 30/04/2015 (Cystic Fibrosis)	A
lomitapide	0/1 (drug already available in 648)	Se	NO	Det AIFA 25/05/2015 (adult patients with homozygous familial hypercholesterolaemia)	A
mannitolo (Bronchitol)	0/7 (minimal efficacy recognized to this drug and, additionally, FC treatment is in charge of Italian Regions)	may 14	NO	Positive opinion CHMP 13/04/2012	n.a.
pomalidomide	4/8	jan 15	NO	Det AIFA 22/07/2015 (relapsed/refractory MM)	H
sofosbuvir	1/1	jul 14	YES	Det AIFA 12/11/2014 (HCV)	A
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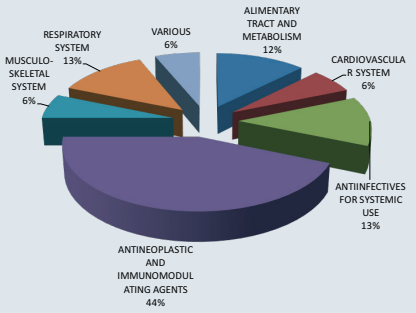
trastuzumab + emtasine	0/2 (suggestion to ask the drug to the Company through DM 8/5/2003)	jun 14	YES	Det AIFA 10/09/2014 (breast HER2+ cancer)	H

Figure 1: distribution for ATC first level code



The products under AIFA's evaluation belong to the following 7 main ATC-classes (Figure 1): A (alimentary tract and metabolism), C (cardiovascular system), J (antinfectives for systemic use), L (antineoplastic and immunomodulants agents), M (muscolo-skeletal system), R (respiratory system) and V (various). The class mainly represented is the L, with 7 of 16 drugs under analysis, followed by A, J and R, with two products each. In terms of number of patients for whom the drugs have been required, the therapeutic areas mainly represented were the respiratory system (cystic fibrosis), the onco-haematology (multiple myeloma and MCL) and other rare diseases (Duchenne muscular dystrophy, short-bowel syndrome, cystic fibrosis, inborn errors of primary bile acid synthesis).

Table 2: patients' access to Fondo for 2013 and 2014

Year	Drug	Disease	n. Pts	n. vials/ packs	€
2013	abiraterone/ Zytiga	Prostate cancer	3	18 packs	89.730 + IVA
	ivacaftor/ Kalydeco	Cystic fibrosis	1	3,2 packs	57.857,13 + IVA
	pomalidomide/ Imnovid	Multiple Myeloma	1	2 packs	19.124 + IVA
2014	ivacaftor/ Kalydeco	Cystic fibrosis	2	6 packs	115.714,26 + IVA
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Patients who got access to Fondo 5% were 5 in 2013 and 4 in 2014.

Results

Over the period under analysis, CTS evaluated 16 drugs (listed in Table 1), for the treatment of 70 patients.

- Out of 69 single applications, 15 were approved, 9 rejected as the product obtained a full registration and reimbursement, 36 rejected (demanded to Ministerial Decree May 8th 2003, or to expanded access programs, or being drugs already included in 648 List), 2 rejected due to the lack of strong scientific data or waiting CHMP's decision, and 8 rejected due to technical reasons.
- The therapeutic areas mainly represented were the respiratory system (cystic fibrosis), the onco-haematology (multiple myeloma and MCL) and other rare diseases (Duchenne muscular dystrophy, short-bowel syndrome, cystic fibrosis, inborn errors of primary bile acid synthesis).

Seven out 16 drugs under evaluation obtained a full authorization in the timeframe taken into account, 4 in reimbursement class H (drugs that must be used only in hospitals) and 3 in class A (essential drugs and those for chronic diseases); all these drugs are fully reimbursed by the NHS. Two drugs are currently classified in class C (Cnn), which includes drugs not yet negotiated. Two other drugs received a recent positive opinion from EMA's CHMP. The remaining five drugs are still not yet available on the Italian market.

Conclusions

AIFA has a very high engagement to assure patient access to orphan and life saving drugs. Analyses show that, excluding isolated cases of lack of scientific data or adequate eligibility criteria, all the patients had access to the required treatment.

Several applications were referred to drugs awaiting market entry, while some others concerned drugs not marketed in Italy, for commercial issues.

This analysis shows that Law 326/2003 is a valuable resource for rare disease patients and, together with Law 648/1996, Law 94/1998 and Ministerial Decree of 8 May 2003, it demonstrates AIFA's commitments to enable better access to orphan diseases to Italian patients.

References

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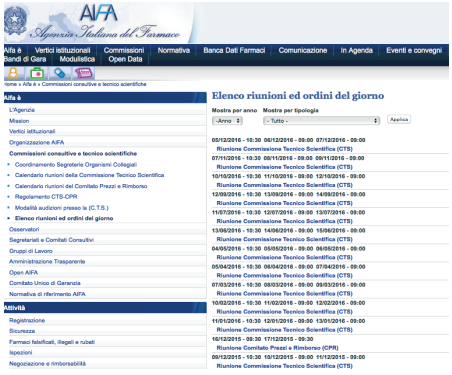

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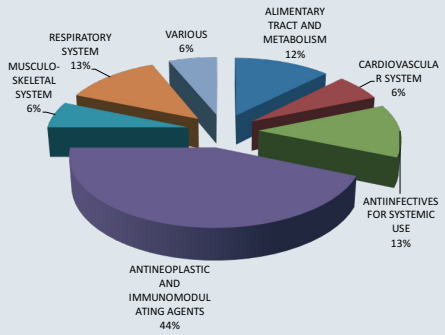

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