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Managed Entry Agreements for orphan drugs in Italy active on April 2016

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Introduction

Managed Entry Agreements (MEAs), monitored by AIFA through the use of specific Monitoring Registries, have been introduced in June 2005. Italy is recognised as one of the pioneers in developing access schemes for new medicines. The prices of reimbursed innovative pharmaceuticals are usually associated with some forms of conditional reimbursement agreement concluded by AIFA and pharmaceutical companies. The aim is to assure access to new medicines for all patients, to maintain the pharmaceutical budget by using these innovative drugs in target disease populations, and to avoid unnecessary expenses to the National Health Service (NHS). Through the AIFA's Monitoring Registries System, it is possible to evaluate the drug utilisation in clinical practice, to gather epidemiologic data, to get information on safety profile or to collect ex-post evaluation about missing knowledge. Actually there are two kinds of active Registries through the AIFA's web system: *Drug Product Registries* (DPR), fully focused on the single drug, its (appropriate) use and impact in terms of cost for the Italian NHS, and *Drug Product Therapeutic Area Registries* (DP TAR) focused on the drug, but within the therapeutic algorithm. The Registry tracks the eligibility of patients, guaranteeing the appropriate use of medicines according to their approved indications and evaluating the effectiveness of treatment in clinical practice. Epidemiology, safety profile, and ex-post evaluation data on any missing information are also added to the Registry. The Managed Entry Agreements between AIFA and Companies are "financial based" (to manage budget impact) or "performance based" (to manage utilisation in real life or to provide evidence regarding uncertain decisions). Some Registries are also aimed to just monitor the appropriateness of drug prescription.

Objectives

The aim of this analysis is to investigate MEAs adopted in Italy on orphan drugs, and the relevant time elapsed from EMA approval to their availability on the Italian market.

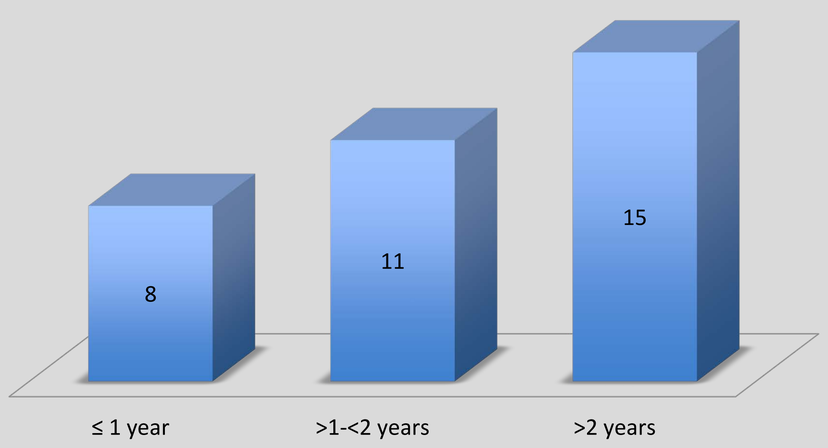
Methods

All the MEAs released by AIFA have been sistematically reviewed, integrating different sources such as AIFA Registries, Gazzetta Ufficiale, EMA website and AIFA's Osmed Report. Data have been gathered for a total of 34 (on a total of 125) products or indications linked to an Orphan Designation, under AIFA's monitoring on April 2016.

Table 1: Types of MEAs linked to typologies of Registries

Brand Name	Active Substance	Therapeutic Area	Registry	MEAs	Start date
REVLIMID	lenalidomide	Multiple Myeloma	DPR	Appropriateness of prescription	09/07/08
REVLIMID	lenalidomide	Leukemia, Myelogenous, Chronic	DPR - Legge 648/96	Appropriateness of prescription	08/08/08
REVLIMID	lenalidomide	Myelodysplastic Syndromes	DPR & DPR - Legge 648/96	Appropriateness of prescription	07/10/08
THALIDOMIDE	talidomide	Multiple Myeloma	DPR	Appropriateness of prescription	11/02/09
ATRIANCE	nelarabina	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	DPR	Appropriateness of prescription	17/11/10
ELAPRASE	idursulfase	Mucopolysaccharidosis II	DPR	Appropriateness of prescription	17/11/10
THALIDOMIDE	talidomide	Multiple Myeloma	DPR - Legge 648/96	Appropriateness of prescription	13/04/11
ADEMPAS	riociguat	Hypertension, Pulmonary	DPR	Appropriateness of prescription	25/08/11
NPLATE	romiplostim	Purpura, Thrombocytopenic, Idiopathic	DPR	Appropriateness of prescription	07/12/11
REVLIMID	lenalidomide	Leukemia, Myelogenous, Chronic	DPR - Legge 648/96	Appropriateness of prescription	30/09/14
ESBRIET	pirfenidone	Idiopathic Pulmonary Fibrosis	DPR	Appropriateness of prescription	01/10/14
KALYDECO	ivacaftor	Cystic Fibrosis	DPR	Appropriateness of prescription	25/12/14
MEPACT	mifamurtide	Osteosarcoma	DPR	Appropriateness of prescription	25/12/14
TASIGNA	nilotinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	DPR	Financial based	23/11/06
ADCETRIS	brentuximab vedotin	Hodgkin Disease	DPR	Financial based	26/11/08
ARZERRA	ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	DPR	Financial based	09/04/09
ADCETRIS	brentuximab vedotin	Lymphoma, Non-Hodgkin	DPR	Financial based	24/05/11
SIRTURO	bedaquilina	Tuberculosis, Multidrug-Resistant	DPR	Financial based	14/06/11
VIDAZA	azacitidina	Myelodysplastic Syndromes	DPR	Financial based	07/12/11
VIDAZA	azacitidina	Acute myeloid leukaemia	DPR	Financial based	07/12/11
DACOGEN	decitabine	Leukemia, Myeloid	DPR	Financial based	08/07/14
NEXAVAR	sorafenib	Carcinoma, Renal Cell	DPR	Financial based	08/07/14
TORISEL	temsirolimus	Lymphoma, Mantle-Cell	DPR	Financial based	01/10/14
SPRYCEL	dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Precursor Cell Lymphoblastic Leukemia-Lymphoma	DPR	Financial based	13/11/14
TORISEL	temsirolimus	Carcinoma, Renal Cell	DPR	Performance based	14/03/08
ICLUSIG	ponatinib	Leukemia, Lymphoid/ Leukemia, Myeloid	**DP TAR**	Performance based	05/06/08
TASIGNA	nilotinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	DPR	Performance based	14/09/10
SIGNIFOR	pasireotide	Hypopituitarism	DPR	Performance based	05/01/11
ICLUSIG	ponatinib	Leukemia, Lymphoid/Leukemia, Myeloid	**DP TAR**	Performance based	09/04/11
YONDELIS	trabectedin	Ovarian Neoplasms	DPR	Performance based	24/05/11
YONDELIS	trabectedin	Sarcoma	DPR	Performance based	24/05/11
MOZOBIL	plerixafor	Hematopoietic Stem Cell Transplantation Lymphoma Multiple Myeloma	DPR	Performance based	29/06/13
BOSULIF	bosutinib	Chronic myeloid leukaemia Ph+	**DP TAR**	Performance based	15/03/15
NEXAVAR	sorafenib	Carcinoma, Hepatocellular	DPR	Performance based	05/05/15

Figure 1: Time between EMA's first approval and Registry activation



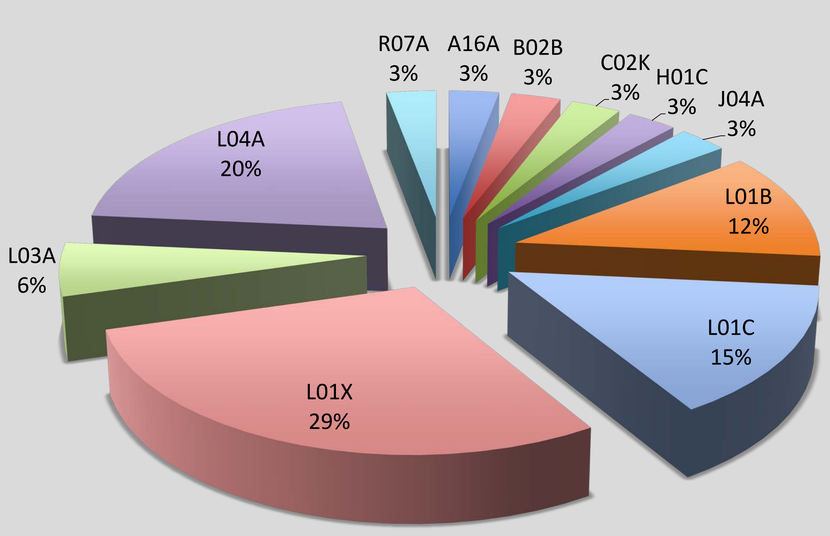
The median time from EMA's first approval and Registry activation is 20 months (range 4-61). 8 of 34 Registries have been activated within one year from EMA's first approval (median 9,5 months, range 4-12): 6/8 are related to oncological drugs, 1 to a drug for pulmonary arterial hypertension and 1 to a drug for treatment of tubercolosis. All the Registries activated within one year from EMA's first approval are linked to DPR, as well as all the 15 approved after two years. 3/11 Registries activated between 1 and 2 years after EMA's approval (Iclusig ALL, Iclusig CML and Bosulif) are DP TAR (the others are all DPR). For three drugs (Adcetris, Iclusig and Thalidomide Celgene) a new Registry has been activated after the closure of the previous one and changing the access conditions.

Table 2: List of MEAs/Registries about drugs/indications linked to an orphan designation active on April 2016

Brand Name	Active Substance	OD disease	OD date
ADCETRIS	brentuximab vedotin	Hodgkin lymphoma	14/01/09
ADCETRIS	brentuximab vedotin	Anaplastic large cell lymphoma	14/01/09
ADEMPAS	riociguat	Pulmonary arterial hypertension	19/12/07
ARZERRA	ofatumumab	Chronic lymphocytic leukaemia	07/11/08
ATRIANCE	nelarabina	Acute lymphoblastic leukaemia	16/06/05
BOSULIF	bosutinib	Chronic myeloid leukaemia	04/08/10
DACOGEN	decitabine	Acute myeloid leukaemia	08/06/06
ELAPRASE	idursulfase	Mucopolysaccharidosis, type II	11/12/01
ESBRIET	pirfenidone	Idiopathic pulmonary fibrosis	16/11/04
ICLUSIG	ponatinib	Chronic myeloid leukaemia	02/02/10
ICLUSIG	ponatinib	Acute lymphoblastic leukaemia	02/02/10
KALYDECO	ivacaftor	Cystic fibrosis	08/07/08
MEPACT	mifamurtide	Osteosarcoma	21/06/04
MOZOBIL	plerixafor	Mobilize prior to stem cell transplantation	20/10/04
NEXAVAR	sorafenib	Renal cell carcinoma	27/09/04
NEXAVAR	sorafenib	Hepatocellular carcinoma	11/04/06
NPLATE	romiplostim	Idiopathic thrombocytopenic purpura	27/05/05
REVLIMID	lenalidomide	Multiple myeloma	12/12/03
REVLIMID	lenalidomide	Mantle cell lymphoma	27/10/11
REVLIMID	lenalidomide	Diffuse large B-cell lymphoma	13/05/11
REVLIMID	lenalidomide	Myelodysplastic syndromes	07/03/04
SIGNIFOR	pasireotide	Cushing's disease	08/10/09
SIRTURO	bedaquilina	Tuberculosis	26/08/05
SPRYCEL	dasatinib	Chronic myeloid leukaemia	23/12/15
TASIGNA	nilotinib	Chronic myeloid leukaemia	22/05/06
TASIGNA	nilotinib	Chronic myeloid leukaemia	22/05/06
THALIDOMIDE	talidomide	Multiple myeloma	20/11/01
THALIDOMIDE	talidomide	Multiple myeloma	20/11/01
TORISEL	temsirolimus	Mantle cell lymphoma	06/11/06
TORISEL	temsirolimus	Renal cell carcinoma	06/04/06
VIDAZA	azacitidina	Myelodysplastic syndromes	06/02/02
VIDAZA	azacitidina	Acute myeloid leukaemia	28/11/07
YONDELIS	trabectedin	Ovarian cancer	17/10/03
YONDELIS	trabectedin	Soft tissue sarcoma	30/05/01

Some drugs (i.e. Tasigna or Thalidomide) have two different active Registries on the same indication, depending on the specific indication (first line, maintenance, etc.).

Figure 2: MEAs and Registries active for ATC-4 code

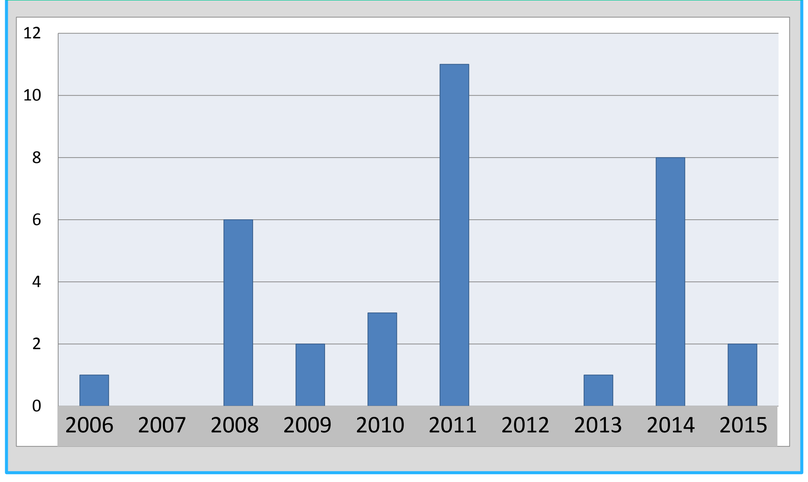


The main represented ATC-4 for products under AIFA's evaluation were: L01X (other antineoplastic agents) 29%, L04A (immunosuppressant) 20%, L01C (Plant alkaloids and other natural products) 15% and L01B (antimetabolites) 12%.

Results

Out of 125 AIFA active Monitoring Registries on April 2016, 34 are related to drugs that obtained orphan designation. The main represented therapeutic area is oncology with 26/34 orphan drugs under monitoring. Out of 34 Registries, only 3 are Drug Product Therapeutic Area Registries (all linked to a performance based MEA). The most frequent type of MEA under monitoring is linked to appropriateness of prescription (13/34), followed by financial based agreements (12/34). All the performance based agreements except one (Signifor, for Cushing's Syndrome) are related to oncological drugs. The 34 Monitoring Registries are about 26 drugs: Yondelis, Iclusig, Vidaza, Adcetris, Thalidomide having 2 Registries differing for specific indication, and Lenalidomide has 4.

Figure 3: Monitoring Registries approved per year



Conclusions

A variety of MEAs, including orphan drugs, are used in Italy in order to manage budget impact and uncertainty around clinical and cost-effectiveness. The use of MEAs represents a significant tool for the management of a sustainable pharmaceutical expenditure and also for the generation of further clinical evidences by Monitoring Registries' adoption. They allow orphan drugs - and especially new and expensive therapies - to be available for the Italian patients, maintaining the difficult balance among sustainability, safety and effectiveness of drugs.

References

- AIFA, Registri Farmaci sottoposti a monitoraggio http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio
- Gazzetta Ufficiale Repubblica Italiana
- EMA http://www.ema.europa.eu/ema/

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