INSTITUTE FOR RARE DISEASES

WWW.RAREDIS.ORG

Maestro Georgi Atanasov Str, 22, BG-4000 Plovdiv // info@raredis.org // +359 32 57 57 97

〉 INFORMATION CENTRE FOR RARE DISEASES AND ORPHAN DRUGS
〉 MEDICAL CENTRE "RAREDIS"
〉 RESEARCH CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND ANALYSES

Issue 4 **July 2013**

ORPHAN DRUGS IN BULGARIA

PERIODIC REVIEW OF THE ACCESS TO ORPHAN DRUGS IN BULGARIA

Methodology

Orphan drug is a medical product if its sponsor can establish:

- **(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or**
  that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;
- **(b) and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.**

The orphan drugs, included in this report, (1) have been orphan designated under the Regulation (EC) No 141/2000 and (2) have marketing authorisation and positive evaluation of significant benefits.

The list is arranged by tradename in alphabetical order, including active substance, ATC code and year or market authorisation, as well information about the presence of the medicine in the Positive drug list (PDL) of Bulgaria.

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Part 1
ORPHAN DRUGS IN THE EUROPEAN UNION

Orphan medicinal products in the European Union (EU) (Table 1) are subject to market authorisation through a centralised procedure under Regulation (EC) 726/2004. Granted authorisation is in force for all 28 Member States.

A key point in analysing the dynamics of the total number of market authorised orphan drugs in the EU (Table 2) is the implementation of Art. 6 of Regulation (EU) 141/2000 – the market exclusivity of orphan drugs. Community and Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product. After the expiration of the 10-year period, however, the European Medicines Agency (EMA) withdraws the orphan status. Logically, this protection from generics has already expired for the orphan drugs approved in the first three years after the adoption of Regulation (EU) 141/2000. Officially, these drugs are no longer orphan. Nevertheless, the current total number of orphan drugs in the EU has not declined – just for example, the number of market authorisations for 2012 is equal to the total number of these ones for 2001-2003.

For the past 12 years EMA has approved for market use an average of 6.25 ± 3.31 orphan drugs per year. During the second half of this period the number almost doubled (Diagram 1) – from 27 (2001-2006) up to 48 (2007-2012). This statistics does not include orphan drugs, whose marketing authorisation has been withdrawn by EMA and thus no longer available on the market.

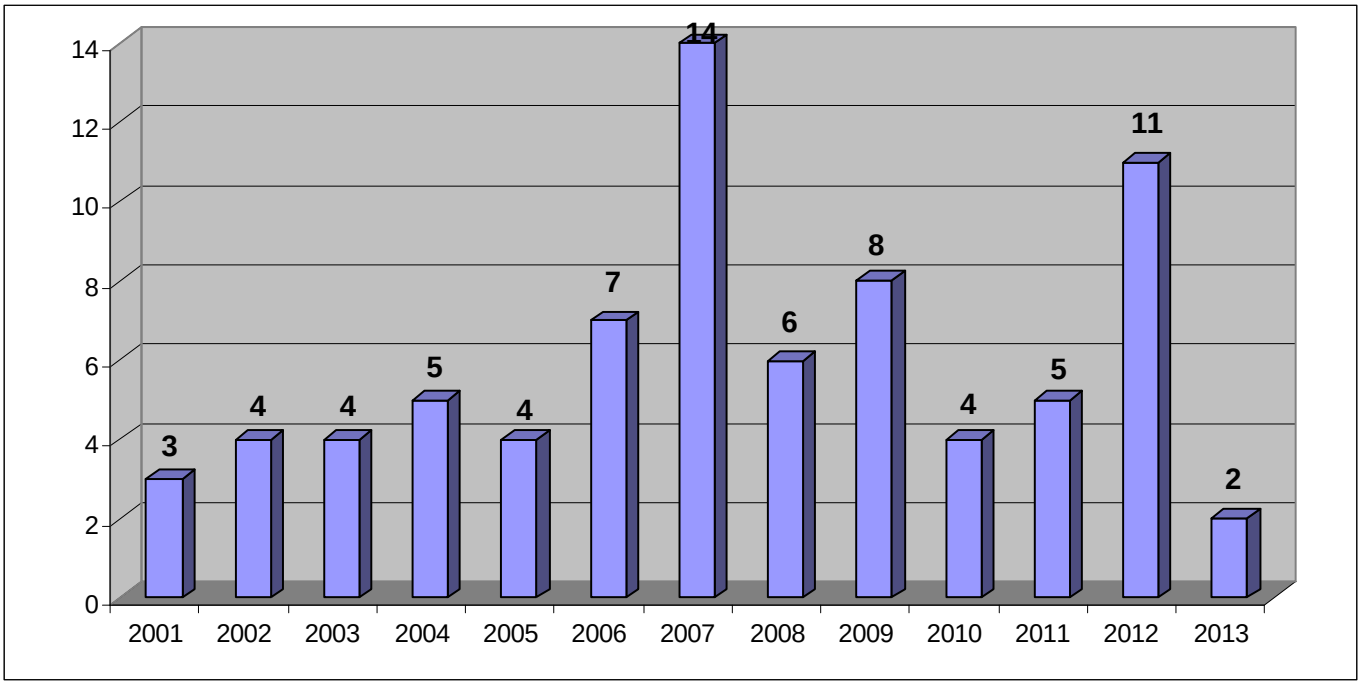

Diagram 1. Annual number of granted market authorisation for orphan drugs by EMA

Additionally, it should be noted that in seven cases, the market authorisation holder has later applied for removing the orphan status (Table 3). Subsequently, the medicinal product has lost some of its "orphan" privileges, but eventually it remains available at the market.

Table 1. Orphan drugs with a valid marketing authorisation in the European Union by July 2013

	TRADE NAME	ACTIVE SUBSTANCE	ATC CODE	YEAR OF MARKET AUTHORISATION
1	Adcetris	brentuximab vedotin	L01XC12	2012
2	Arzerra	ofatumumab	L01XC10	2010
3	Atriance	nelarabine	L01BB07	2007
4	Bosulif	bosutinib	L01XE14	2013
5	Bronchitol	mannitol	R05CB16	2012
6	Cayston	aztreonam lysine	J01DF01	2009
7	Ceplene	histamine dihydrochloride	L03AX14	2008
8	Cystadane	betaine anhydrous	A16AA06	2007
9	Dacogen	decitabine	L01BC08	2012
10	Diacomit	stiripentol	N03AX17	2007
11	Elaprase	idursulfase	A16AB09	2007
12	Esbriet	pirfenidone	L04AX05	2011
13	Evoltra	clofarabine	L01BB06	2006
14	Exjade	deferasirox	V03AC03	2006
15	Firazyr	icatibant	C01EB19	2008
16	Firdapse	amifampridine	N07XX05	2009
17	Gliolan	5-aminolevulinic acid hydrochloride	L01XD04	2007
18	Glybera	alipogene tiparvovec	C10AX10	2012
19	Iclusig	ponatinib	L01XE24	2013
20	Increlex	mecasermin	H01AC03	2007
21	Inovelon	rufinamide	N03AF03	2007
22	Jakavi	ruxolitinib (as phosphate)	L01XE18	2012
23	Kalydeco	ivacaftor	R07AX02	2012
24	Kuvan	sapropterin dihydrochloride	A16AX07	2008
25	Litak	cladribine	L01BB04	2004
26	Lysodren	mitotane	L01XX23	2004
27	Mepact	mifamurtide	L03AX15	2009
28	Mozobil	plerixafor	L03AX16	2009
29	Myozyme	alglucosidase alfa	A16AB07	2006
30	Naglazyme	galsulfase	A16AB08	2006
31	Nexavar	sorafenib	L01XE05	2006
32	NexoBrid	concentrate of proteolytic enzymes enriched in bromelain	pending	2012
33	Nplate	romiplostim	B02BX04	2009
34	Orfadin	nitisinone	A16AX04	2005
35	Pedea	ibuprofen	C01EB16	2004
36	Peyona	caffeine citrate	N06BC01	2009
37	Plenadren	hydrocortisone	H02AB09	2011
38	Prialt	ziconotide	N02BG08	2005
39	Revatio	sildenafil	G04BE03	2005
40	Revestive	teduglutide	A16AX08	2012
41	Revlimid	lenalidomide	L04AX04	2007
42	Savene	dexrazoxane	V03AF02	2006
43	Signifor	pasireotide diaspartate	H01CB05	2012
44	Siklos	hydroxycarbamide	L01XX05	2007
45	Soliris	eculizumab	L04AA25	2007
46	Sprycel	dasatinib	L01XE06	2006
47	Tasigna	nilotinib	L01XE08	2007
48	Tepadina	thiotepa	L01AC01	2010
49	Thalidomide Celgene	thalidomide	L04AX02	2008
50	Tobi Podhaler	tobramycin	J01GB01	2011

	TRADE NAME	ACTIVE SUBSTANCE	ATC CODE	YEAR OF MARKET AUTHORISATION
51	Torisel	temsirolimus	L01XE09	2007
52	Ventavis	iloprost	B01AC11	2003
53	Vidaza	azacitidine	L01BC07	2008
54	Volibris	ambrisentan	C02KX02	2008
55	Votubia	everolimus	L01XE10	2011
56	Vpriv	velaglucerase alfa	A16AB10	2010
57	Vyndaqel	tafamidis	N07XX08	2011
58	Wilzin	zinc	A16AX05	2004
59	Xagrid	anagrelide	L01XX35	2004
60	Xaluprine	6-mercaptopurine monohydrate	L01BB02	2012
61	Yondelis	trabectedin	L01CX01	2007

Table 2. Medicinal products with withdrawn orphan status (expired 10-year period of market exclusivity) by July 2013

	TRADE NAME	ACTIVE SUBSTANCE	ATC CODE	YEAR OF MARKET AUTHORISATION
1	Aldurazyme	laronidase	A16AB05	2003
2	Busilvex	busulfan	L01AB01	2003
3	Carbaglu	carglumic acid	A16AA05	2003
4	Fabrazyme	agalsidase beta	A16AB04	2001
5	Replagal	agalsidase alfa	A16AB03	2001
6	Somavert	pegvisomant	H01AX01	2002
7	Tracleer	bosentan monohydrate	C02KX01	2002
8	Trisenox	arsenic trioxide	L01XX27	2002
9	Zavesca	miglustat	A16AX06	2002

Table 3. Medicinal products with withdrawn orphan status (by a request of the market authorisation holder) by July 2013

	TRADE NAME	ACTIVE SUBSTANCE	ATC CODE	YEAR OF MARKET AUTHORISATION
1	Afinitor	everolimus	L01XE10	2009
2	Glivec	imatinib	L01XE01	2001
3	Ilaris	canakinumab	L04AC08	2009
4	NovoThirteen	catridecacog	B02BD11	2012
5	Revolade	eltrombopag	B02BX05	2010
6	Sutent	sunitinib	L01XE04	2007
7	Xyrem	sodium oxybate	N07XX04	2005

Part 2
ORPHAN DRUGS IN BULGARIA

While the decision of market authorisation for orphan drugs is taken at European level by EMA, national authorities regulate access to these medicinal products at national level. The reimbursement by public funds is so far the only way that an orphan drug is accessible in Bulgaria. Given the high cost of this type of medicinal products, there is no real possibility for individual patients to pay for them.

The reimbursement decision-making procedure includes pricing and inclusion in the Positive Drug List (PDL). Medicinal products, listed in PDL's Appendix 1 (Medicinal products for treatment of conditions which is paid under the Health Insurance Act) are covered by the National Health Insurance Fund (NHIF) and those, listed in PDL's Annex 2 – by the hospitals' budget under Articles 5, 9 and 10 of the Medical Establishments Act. It should be noted that there were no significant changes in medicinal product reimbursement legislation last year. The last major amendment was in early 2012 when part of oncology drugs (including some orphan medicinal products) was transferred for NHIF coverage.

From the 61 market approved orphan drugs in the EU by July 2013, PDL of Bulgaria includes one (1) in Appendix 1, 7 (seven) in Appendix 2, and ten (10) in both Appendices (Table 4).

Table 4. Reimbursement status in Bulgaria of orphan drugs with a valid market authorisation in the European Union by July 2013

	TRADE NAME	ACTIVE SUBSTANCE	ATC CODE	YEAR OF MARKET AUTHORISATION	PDL A1	PDL A2
1	Elaprase	idursulfase	A16AB09	2007	yes	yes
2	Evoltra	clofarabine	L01BB06	2006	-	yes
3	Exjade	deferasirox	V03AC03	2006	yes	yes
4	Litak	cladribine	L01BB04	2004	-	yes
5	Lysodren	mitotane	L01XX23	2004	-	yes
6	Mozobil	plerixafor	L03AX16	2009	-	yes
7	Myozyme	alglucosidase alfa	A16AB07	2006	yes	yes
8	Nexavar	sorafenib	L01XE05	2006	yes	yes
9	Nplate	romiplostim	B02BX04	2009	-	yes
10	Revatio	sildenafil	G04BE03	2005	yes	-
11	Sprycel	dasatinib	L01XE06	2006	yes	yes
12	Tasigna	nilotinib	L01XE08	2007	yes	yes
13	Tobi Podhaler	tobramycin	J01GB01	2011	yes	yes
14	Torisel	temsirolimus	L01XE09	2007	-	yes
15	Ventavis	iloprost	B01AC11	2003	yes	yes
16	Volibris	ambrisentan	C02KX02	2008	yes	yes
17	Vyndaqel	tafamidis	N07XX08	2011	yes	yes
18	Yondelis	trabectedin	L01CX01	2007	-	yes

Despite the dynamics in the number of orphan drugs at Community level (newly approved orphan drugs and drugs with withdrawn orphan status in 2013), there are no significant changes in the level of access to these therapies in Bulgaria, compared to 2012 (Diagram 2).

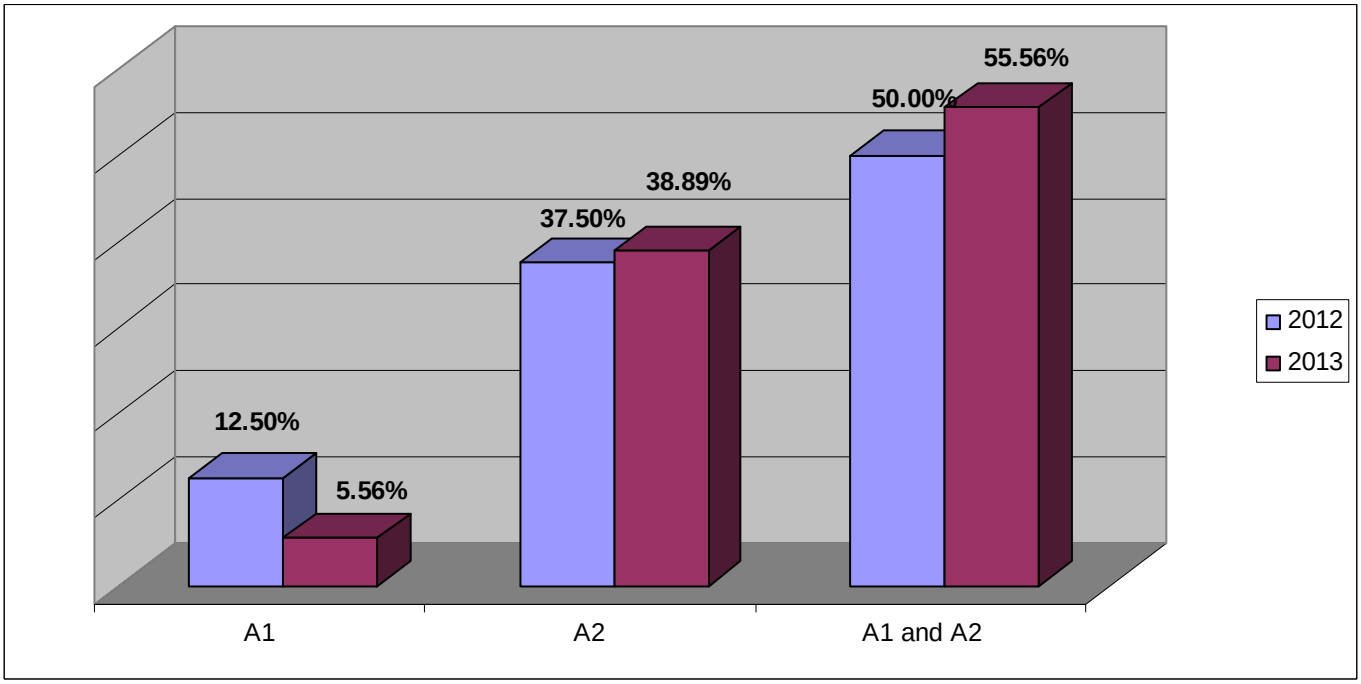

Diagram 2. Dynamics of access to orphan drugs in Bulgaria for 2012-2013

Out of PDL's Appendices, orphan drugs are virtually inaccessible for the Bulgarian rare diseases patients (Diagram 3). The change in the relative share of the orphan drugs, that are not accessible in Bulgaria in 2013 compared to 2012 (+ 6.31%), is mainly explained by the fact that some of the previously (and still) reimbursed drugs are no longer orphan-labeled, as well as the market authorisation holders of the newly approved ones in 2012 and 2013 have not yet submitted documents for inclusion in PDL of Bulgaria.

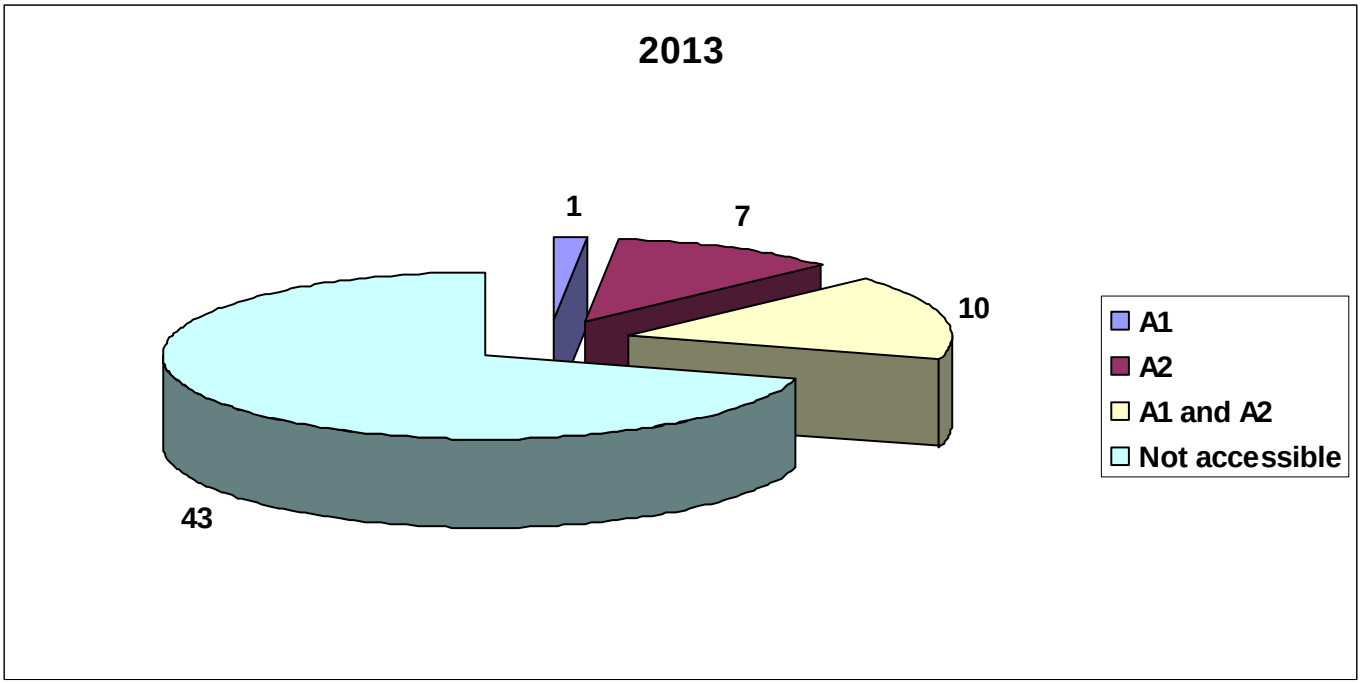

Diagram 3. Orphan drugs in Bulgaria by July 2013

The inclusion/removal dynamics is shown on Table 5. Two new orphan drugs have been approved for reimbursement, while two previously reimbursed ones have been excluded from further coverage by NHIF.

Table 5. Included and removed orphan drugs (no orphan status change) of PDL for 2012-2013

	TRADE NAME	ACTIVE SUBSTANCE	INDICATION	YEAR OF MARKET AUTHORISATION
	Myozyme	alglucosidase alfa	Pompe disease	2006
	Vyndaqel	tafamidis	Transthyretin amyloidosis	2011
	Atriance	nelarabine	T-cell acute lymphoblastic leukaemia T-cell lymphoblastic lymphoma	2007
	Xagrid	anagrelide	Essential thrombocythaemia	2004

SUMMARY

Since the first review of the access to orphan drugs in 2010 to now, findings have always confirmed an increasing trend in the share of reimbursed orphan drugs in Bulgaria. In 2013, however, a kind of stagnation is observed for the first time. Two new drugs have become available, but two others are no longer reimbursed. The fact that the orphan status has been revoked or withdrawn of some these medicinal products, that are already available in Bulgaria, has also impacted these numbers. However, it is too early to draw conclusions about changes in access to orphan drugs in the country.

Patients with rare diseases have the legitimate right to equal and fair access to health care. As a result of the policies in the field of rare diseases, these people want to see increased life expectancy and improved quality of life. Adequate access to orphan drugs is one of the many mutually reinforcing ways to achieve this goal.

ANNEX
References

- **European Commission, DG SANCO**
  Register of designated orphan medicinal products
  (http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm)
- **European Commission, DG SANCO**
  Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
  http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf
- **European Commission, DG SANCO**
  Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:EN:PDF
- **European Medicines Agency**
  Register of medicinal products
  http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124&jsenabled=true
- **Ministry of Health**
  Ordinance on the conditions, rules and procedures for medical product pricing
  http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=391&categoryid=5874
- **Ministry of Health**
  Positive drug list of Bulgaria
  http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=517&categoryid=5753
- **National Health Insurance Fund**
  List of medicinal products, covered by NHIF
  http://services.nhif.bg/NZOK_References/faces/lists/medicine.jsp
- **Iskrov G, Miteva-Katrandzhieva T, Stefanov R.** Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria. Health Policy. 2012 Nov;108(1):10-8.
  http://www.healthpolicyjrnl.com/article/PIIS0168851012002229/abstract
- **Information Centre for Rare Diseases and Orphan Drugs**
  Review of the access to medicines for rare diseases in Bulgaria, 2010
  http://raredis.org/pub/OD%20Report%2022072010%20EN.pdf
- **Information Centre for Rare Diseases and Orphan Drugs**
  Review of the access to medicines for rare diseases in Bulgaria, 2011
  http://raredis.org/pub/OD_Report_04042011_EN.pdf
- **Information Centre for Rare Diseases and Orphan Drugs**
  Review of the access to medicines for rare diseases in Bulgaria, 2012
  http://raredis.org/pub/OD_Report_2012_EN.pdf