ACCESS TO MEDICINES FOR THE TREATMENT OF RARE DISEASES: THE BULGARIAN REALITY

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Introduction

Rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in EU. Most of the people in EU are actually affected by less frequently occurring diseases (1 in 100,000). The medicinal products which are intended for the diagnosis, prevention or treatment of rare diseases are known as orphan drugs. The pharmaceutical industry has little interest in developing and marketing orphan medicines (1,2,3). The patients should be entitled to the same quality of treatment (4). In order to stimulate the R&D and bringing to the market orphan drugs the European Parliament and the EU Council have established Community procedure for designation of as orphan medicinal products status.

GOAL

The aim of our study is to analyze the Bulgarian regulatory policy for orphan medicines and rare diseases, and it's consistency with EU policies

Materials and methods

The current publication reviews and analysis the following EU and Bulgarian legislation:
Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs;
Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definition of the concepts "similar medicinal product" and "clinical superiority. It was reviewed the Health law, Law on medicines in human medicine, Regulation No22/2005 on orphan drugs, Regulation on criteria, conditions and rules for inclusion of medicinal, Products in positive list, Regulation 34/2005, The current Positive Drug List in Bulgaria.
The above documents have been reviewed and analyzed from the perspective of their relation to diagnosis, prevention and treatment of rare disease and orphan drug and their role for improving the access to adequate treatment. The Positive list was reviewed for ICD codes that correspond to rare diseases (according to the data available in www.orpha.net (3) and only the treatment of rare diseases was analyzed from the perspective of both with orphan drugs and with other medicines.

Results

Regulation on orphan drugs in the European Union

No specific legislation was created on Community level until 22 January 2000 when the Orphan Medicinal Product Regulation (Regulation (EC) 141/2000) was published.
Regulation (EC) 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products sets up criteria for orphan drug designation in EU and describes the incentives in the Introduction part which are implemented to encourage the research, development and marketing of orphan drugs (4). The main requirements of Regulation (EC) 141/2000 are described in Table 1:
Commission Regulation (EC) No 847/2000 is defining the concepts "similar medicinal product" and "clinical superiority" and it is intended to assist potential sponsors, the Committee for Orphan Medicinal Products, and competent authorities in the interpretation of Regulation (EC) No 141/2000. This regulation specifies the criteria for designation and definitions such as "significant benefit" for the purpose of implementation of art. 3 of Regulation No141/2000; "active substance", "similar medicinal product", "similar active substance" for the purposes of implementation of article 8 of Regulation (EC) No 141/2000, "clinically superior" etc.
Regulation (EC) No 141/2000 and Commission Regulation (EC) No 847/2000 provide the legislative frame for orphan drugs and rare diseases setting up the Community procedure for designation of orphan drugs and incentives to the sponsors on a Community level.
The treatment of rare diseases and the improvement of quality of life of the affected by rare disease people in EU depends not only on legislation available but on development and implementation of common strategies, in Europe. Rare diseases are one of the priorities in the current EU Public Health Program running till 2013 and the oriented in 3 main fields: improving recognition and visibility on rare diseases, supporting policies on rare diseases in Member states and developing European cooperation, coordination and regulation for rare diseases. It was created Orphanet, Eurordis and several networks of clinical centers cooperating to develop information services or to coordinate their clinical activities (5). In addition, an EU Rare Disease Task Force was established.

Bulgarian legislation on orphan drugs and rare diseases and transposition of EU legislation of orphan drugs in Bulgaria

For its 7 5000 000 population (official data as of 2004) the patients suffering from rare diseases is estimated 400 - 450 000 people. There are 6 medical management centers in the country for diagnosis and treatment of rare diseases in Bulgaria (6). The national legislation on orphan drugs comprises of several laws and regulations (6) presented in Table 2. The Health law outlines the genetic examinations and prenatal tests which are aimed to limit the incidence of rare diseases in the country. The Law on medicines refers to Regulation (EC) 141/2000 and sets up the conditions for marketing authorization of orphan drugs, their pricing and reimbursement. These drugs are included into the Positive list and are covered by the Health insurance fund or the state budget.

Table 1. Main requirements of Regulation (EC) 141/2000

Article	Requirements
Article 3. Criteria for designation **Article 4. Committee for Orphan Medicinal Products (COMP)**	Includes the criteria for orphan drug designation. COMP is set within EMEA with the following tasks: to examine any application for the designation of a medicinal product as an orphan product, to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union, to assist the Commission in liaising internationally on matters relating to orphan medicinal products and to assist the Commission in preparation of detailed guidelines.
Article 5. Procedure for designation and removal from the register	After submission of application by the sponsor to EMEA, together with required documentation, the COMP gives opinion about the designation within 90 days of the receipt of the valid application. The designated medicinal product is entered in the Community Register of Orphan Medicinal Products. Each year, the sponsor submits to EMEA a report on the state of development of the designated product.
	Incentives for the sponsors
Article 6. Protocol assistance	The sponsor of an orphan medicinal may, prior to the submission of an application for the marketing authorization request advice from the EMEA on the conduct of the various tests and clinical trials necessary to demonstrate the quality, safety and efficacy of the medicinal product.
Article 7. Community marketing authorization	The person responsible for placing an orphan medicinal product on the market may request the authorization to be granted with the provisions of Centralized Procedure without having to justify that the medicinal product qualifies under Part B of the Regulation. Reductions of the fees payable to EMEA are offered to the sponsors.
Article 8. Market exclusivity	Where a marketing authorization in respect of an orphan medicinal product is granted, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product. This period may be reduced to six years if the criteria are no longer met.
Article 9. Other incentives	Medicinal products designated as orphan medicinal products shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan products and in particular aid for research for small- and medium-size undertakings.

Table 2. Bulgarian legislation concerning rare diseases/orphan drugs

Law/regulation	Scope of the document	Relation to rare diseases/orphan drugs
Health law	public health protection relations	• **Chapter 4 "Health protection of specific populations", section 2 "Reproductive health", paragraph 127 (2),p.5** requires prenatal diagnostics and prophylaxis of genetic diseases. • **Chapter 4 "Health protection of specific populations", section 4 "Genetic health and genetic examinations", paragraph 137-144** requires treatment prophylaxis and diagnostics of genetic diseases, treatment of inherited diseases
Law on medicinal products in human medicine	Marketing authorization of medicinal products, licensing of pharmaceutical manufacturers, wholesalers, retailers, clinical trials, advertizing, classification, pharmacovigilance, state control over the market, pricing of medicinal products and reimbursement.	• **Chapter 3 "Marketing authorization",, paragraph 25 (1):** reference to Regulation (EC) 141/2000 regarding the criteria for orphan drug and **paragraph 25 (2)** which is reference to Regulation 762/2004 with regard to marketing authorization of orphan drugs. • **Chapter 3 "Marketing authorization", paragraph 27**, regarding the proof of orphan drug designation required as submission documentation for marketing authorization. • **Chapter 12 "Pricing of medicinal products", paragraph 262, (4), p.4**: orphan drugs are part of the "positive" list (the reimbursement list). • Definition of orphan drug is given.
Regulation No22/2005	Orphan drugs marketing authorization	Regulates the criteria for orphan drug designation and requirements for orphan drug designation which are harmonized with EU requirements.
Regulation No 34 as of 25.11.2005	Lays down the provisions for prescribing, dispatching the products for treatment of diseases which are excluded from the obligatory health insurance.	According to Regulation 34/2005, article 2, (1),p.4 the treatment of rare diseases is paid by the Ministry of health.
Regulation on criteria, conditions and rules for inclusion of medicinal products in PDL	Lays down the provisions for inclusion of medicinal products into the Positive list.	Regulates the inclusion of drugs into a positive list, including the drugs for the treatment of rare diseases.

Bibliography

1. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on rare diseases: Europe's challenges
2. "Orphan drugs and rare diseases at a glance", Doc. Ref. EMEA/290072/2007, European Medicines Agency
3. www.orpha.net
4. Regulation (EC) 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
5. Ségolène Aymé , J. Schmidtke "Networking for rare diseases: a necessity for Europe ", Bundesgesundheitsblatt - Gesundheitsforschung – Gesundheitsschutz, vol.50, number 12, December 2007, 1477-1483
6. Ministry of health. National Program for rare diseases (2009-2013) (genetic, malformations and non heredity diseases), MoH Bulgaria

Results

Positive Drug List and availability of treatment of rare diseases

The Positive list was analyzed from the perspective of availability of rare diseases in the annexes (as determined in www.orpha.net) and the access of the Bulgarian patients to an adequate treatment.
There are 4 annexes of the Positive as follows:
Annex 1: Medicinal products covered by the National healthcare fund (intended for home treatment of the diseases which are covered by the health insurance package);
Annex 2: Medicinal products covered by the hospital budget (intended for hospital treatment);
Annex 3:Medicinal products intended for treatment of diseases which are not covered by the obligatory health insurance and are paid from the state budget
Annex 4: Medicinal products intended for treatment of rare diseases, AIDS and treatment and prophylaxis of infection diseases.
Our study is focused on Annexes 1,3 and 4 as they include medicinal products available for continuous out-hospital treatment.
Annex 1 contains medicinal product intended for ambulatory treatment. We have found that it contains 39 ICD codes of diseases which presence allow patients to receive symptomatic and supportive treatment. Actually for the majority of the diseases in Annex 1 there are no orphan drugs designated. The treatment of two diseases (acromegaly and pulmonary arterial hypertension) is covered 100% by Annex 4, but Annex 1 provided additional supportive treatment. The orphan drugs Levodopa and Carbidopa are reimbursed 100% for the patients with Parkinson's disease.
32 rare diseases are included in Annex 3 and their treatment is covered 100% by the state budget. Most of them are various kinds of malignant diseases, syndromes etc. treated with supportive and symptomatic drugs.
There are no orphan drugs designated for 14 diseases. For 11 diseases there are orphan drugs are designated, but either not available in Bulgaria nor not reimbursed and therefore not affordable for the Bulgarian patients.
Patients, suffering form 7 diseases have access to orphan drugs received designation from COMP.
Treatment of 6 rare diseases is covered with Annex 4 (acromegaly, galactosemia, N-acetyl-alpha-D-galactosaminidase deficiency, cystic fibrosis, pulmonary arterial hypertension, acute respiratory distress syndrome and Turner syndrome). For two of the diseases (acromegaly and pulmonary arterial hypertension) the drugs received orphan designation are reimbursed – pegvisomant and sidlenafil and iloprost respectively.

Table 3. Rare diseases which are present in the Positive Drug List, Annex 1 by the ICD code

ICD code	Rare disease name	Access to treatment and % of reimbursement	Orphan drugs availability
B35.0 B67 B67.5 D69.3	Kerion celsi Hydatidosis Alveolar echinococcosis Thrombocytopenic purpura, autoimmune	Terbinafin (25%) Albendazole (100%) Albendazole (100%) Methylprednisolone, Prednisone (50%)	**No orphan drug is designated.** **No orphan drug is designated.** **No orphan drug is designated.** **2 orphan drugs are designated but not available in Bulgaria.**
E03.0	Hypothyroidism, congenital	Levothyroxine sodium (100%)	**No orphan drug is designated.**
E11	Rabson-Mendenhall syndrome	Insulin Human, Insulin Lispo, Insulin aspart, Insulin glulisine, Insulin glargina, Insulin detemir, Metformin, Glibenclamide,Gliclazide,Glipizide,Glimepiride, Metformin hydrochloride/ Rosiglitazone, Acarbose, Rosiglitazone, Sitagliptin Exenatide Glucagon, (100%) Repaglinide (50%) Thioctic acid, Simvastatin (25%)	**No orphan drugs are designated.**
E22	Acromegaly	Bromocriptine (100%)	**Orphan drug is designated and available under Annex 4.**
E22.8	Microcephaly - hypergonadotropic hypogonadism	Bromocriptine (100%) Leuprorelin, Triptorelin (50%)	**No orphan drugs are designated.**
E23.2 E24	Diabetes insipidus, non-acquired, central Cushing syndrome, Hypercortisolism Hyperadrenocorticism	Desmopressin (100%) Bromocriptine (100%)	**No orphan drugs are designated.** **No orphan drugs are designated.**
E27.1 E83.3	Addison disease Glucocorticoid deficiency, familial Hypophosphatasia, Rathburn disease Phosphoethanolaminuria	2 mg betamethasone as disodium phosphate and 5 mg betamethasone as dipropionate (25%) Methylprednisolone, Prednisone (50%) Calcitriol (100%)	**No orphan drugs are designated.** **1 orphan drug is designated but not available.**
F31	Bipolar disorders	Risperidone, alprazolam , Quetiapine, Olanzapine, Zuclopenthi-xol, Flupentixol, Ziprasidone, Fluphena-zine,Haloperidol, Biperiden, Valproic acid, Carbamazepine	**No orphan drugs are designated.**
G20	Parkinson disease, familial form	Carbidopa/ Levodopa, Levodopa/Benserazide, Pramipe-xole,Entacapone,Rasagiline, Selegiline,Cabergoline, Ropinirole, Apomorphine hydrochloride (inhalation use), Biperiden	**Levodopa and Carbidopa (gastroenteral use) – advanced idiopatic Parkinson's disease with severe motor fluctuations and not repsonding to oral treatment.**
G35	Multiple sclerosis	Tizanidine, Tolperisone Hydrochloride, Flunarizine (25%) Methylprednisolone, Prednisone (50%) Interferon beta - 1 a, Interferon beta-1b (100%)	**No orphan drugs are designated.**
G54.5	Parsonage-Turner syndrome	Diclofenac, Acerclofenac, Tolperisone Hydrochloride (25%) Galantamine (75%)	**No orphan drugs are designated.**
G70.0	Myasthenia gravis,	Pyridostigmine (100%) Galantamine (75%) Prednisone (50%) Tolperisone Hydrochloride (25%)	**1 orphan drug is designated but not available in Bulgaria.**
G71.1	Isaacs-Mertens syndrome, Schwartz-Jampel syndrome	Tolperisone Hydrochloride (25%) Galantamine (75%)	**No orphan drugs are designated.**
G71.2	Arthrogryposis due to muscular dystrophy	Tolperisone Hydrochloride (25%) Galantamine (75%)	**No orphan drugs are designated.**
H16.3	Cogan syndrome	Methylprednisolone,Prednisolone, Tobramycin, Fluorometholone, Dexamethasone; Tobramycin (50%)	**No orphan drugs are designated.**
H41.1	Glaucoma, hereditary	Phenylephrine (25%) Dorzolamide,Brinzolamide (50%) Travoprost, Latanoprost, Latanoprost/Timolol, Betaxolol, Timolol maleate (100%)	**No orphan drugs are designated.**
I10	Brachydactyly - arterial hypertension	Moxonidine, Rilmenidine, Prazosin, Doxazosin, Hydrochlorothiazide,Chlortalidone, Indapamide, Spironolactone, Propranolol, Nitrendipine, Lacidipine, Verapamil, Diltiazem, Enalapril maleate, Lisinopril, Perindopril, Ramipril, Quinapril, Cilazapril, Fosinopril, Trandolapril , Moexipril hydrochloride, Zofenopril calcium, Losartan, Eprosartan, Valsartan, Candesartan, Telmisartan (25%) Methyldopa,Furosemide, Triamterene, Hydrochlorothiazide, Metoprolol tartrate, Atenolol, Bisoprolol Nebivolol, Carvedilol, Bisoprolol/Hydrochlorothiazide, Amlodipine (as amlodipine besilate), Felodipine, Nifedipine, Lercanidipine hydrochloride, Trandolapril/ verapamil, Enalapril maleate/Hydrochlorothiazide, Enalapril maleate; Hydrochlorthiazide, Lisinopril; Hydrochlorothiazide, Perindopril/ Indapamide, Ramipril/ hydrochlorothiazide, Quinapril/Hydrochlorothiazide, Fosinopril; Hydrochlorothiazide, Perindopril arginine/ Amlodipine, Lisinopril/ Amlodipine, Losartan; Hydrochlorothiazide, Eprosartan/ Hydrochlorothiazide, Valsartan/ Hydrochlorothiazide, Telmisartan/Hydrochlorothiazide, Aliskiren, Amlodipine/ Valsartan, Amlodipine/Atorvastatin (50%) Clonidine (75%)	**No orphan drugs are designated.**
I12.0	Mesangial sclerosis, diffuse, Nephrotic syndrome with diffuse mesangial sclerosis	Moxonidine, Rilmenidine, Prazosin, Doxazosin, Hydrochlorothiazide, Chlortalidone, Indapamide, Spironolactone,Propranolol, Nitrendipine, Lacidipine, Verapamil, Diltiazem, Enalapril maleate, Lisinopril, Perindopril, Ramipril, Quinapril, Cilazapril, Fosinopril, Trandolapril, Moexipril hydrochloride, Zofenopril calcium, Losartan, Eprosartan, Valsartan, Candesartan, Telmisartan (25%) Furosemide, Triamterene, Hydrochlorothiazide, Metoprolol tartrate, Atenolol, Bisoprolol, Nebivolol, Carvedilol, Bisoprolol/Hydrochlorothiazide, Amlodipine (as amlodipine besilate), Felodipine, Nifedipine, Lercanidipine hydrochloride, Trandolapril/ verapamil, Enalapril maleate/ Hydrochlorthiazide, Enalapril maleate; Hydrochlorthiazide, Lisinopril; hydrochlorothiazide, Perindopril/ Indapamide, Ramipril/ hydrochlorothiazide, Quinapril/Hydrochlorothiazide, Fosinopril; Hydrochlorothiazide, Perindopril arginine/ Amlodipine, Lisinopril/ Amlodipine, Losartan; Hydrochlorothiazide, Eprosartan/ Hydrochlorothiazide , Valsartan/ Hydrochlorothiazide, Telmisartan/Hydrochlorothiazide, Aliskiren, Amlodipine/ Valsartan, Amlodipine/Atorvastatin (50%)	**No orphan drugs are designated.**
I27.0 I45.6 I47.1	Pulmonary arterial hypertension Wolff-Parkinson-White syndrome Chaotic atrial tachycardia	Isosorbide dinitrate, Pentoxifylline (25%) Acenocoumarol (50%) Propranolol, Verapamil (25%) Acenocoumarol, Sotalol hydrochloride, Metoprolol tartrate, Atenolol (50%) Digoxin (75%) Acenocoumarol, Quinidine sulphate, Propafenone, Amiodarone, Sotalol hydrochloride, Metoprolol tartrate, Atenolol (50%)	**Orphan drug is designated and available under Annex 4.** **No orphan drugs are designated.** **No orphan drugs are designated.**
I48	Atrial fibrillation, familial	Propranolol, Verapamil (25%) Digoxin (75%) Acenocoumarol, Quinidine sulphate, Propafenone, Amiodarone, Sotalol hydrochloride, Metoprolol tartrate, Atenolol (50%) Propranolol, Verapamil (25%)	**No orphan drugs are designated.**
I73.1	Buerger's disease, Thromboangiitis obliterans	Pentoxifylline, Nicergoline, Naftidrofuryl, Naftidrofuryl hydrogen oxalate, Tolperisone Hydrochloride (25%) Acenocoumarol (50%)	**No orphan drugs are designated.**
K20	Eosinophilic esophagitis	Ranitidine, Famotidine, Omeprazole, Lansoprazole, Esomeprazole, Metoclopramide (25%),	**No orphan drugs are designated.**
K50	Corticosteroid-sensitive aseptic abscesses; Crohn disease	Budenoside, Sulfasalazine, Mesalazine (50%)	**No orphan drugs are designated.**
L10.0	Pemphigus vulgaris	Methylprednisolone, Prednisone, Prednisone (50%)	**No orphan drugs are designated.**
M05.0	Felty syndrome	Leflunomide, Rituximab (75%) Sulfasalazine, Methylprednisolone, Prednisolone, Methylprednisolone,Lidocaine, Prednisone, Etanercept, Adalimumab, Tetrazepam (50%) Chloroquine , Diclofenac, Aceclofenac, Meloxicam, Ibuprofen, Dexetoprofen, Etoricoxib, Nimesulide (25%)	**No orphan drugs are designated.**

Table 4. Rare diseases which are present in the PDL, annex 3 by the ICD code-100% reimbursed

ICD code	Rare disease	Available reimbursed local treatment	Orphan drugs availability
C11 C15	Nasopharyngeal cancer Esophageal carcinoma	Cetuximab, Mitomycin, Ondasetron, Granisetron, Palonosetron,Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine,Fentanyl, Pethidine hydrochloride Cetuximab, Mitomycin, Bleomycin, Ondasetron, Granisetron,Palonosetron, Tropisetron , Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.** **No orphan drugs are designated. Access to local treatment only.**
C16	Gastric cancer, Stomach cancer	Capecitabine, Mitomycin, Ondasetron Granisetron, Palonosetron, Tropisetron, Capecitabine,Methylpredni-solone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**Tegafur, EU designation date: 20/12/2007, authorized in Bulgaria, but not reimbursed.** **Other 2 drugs received orphan designation but not available in Bulgaria.**
C25	Pancreatic carcinoma, familial	Erlotinib, Mitomycin, Ondasetron Granisetron, Palonosetron, Tropisetron, Gemcitabine,Methyl-prednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**The available but not reimbursed orphan drugs in Bulgaria are: Paclitaxel, EU designation date: 31/10/2006 and Cisplatin, EU designation date: 08/06/2007.** **Another 14 medicinal products are designated as orphan products but not available in Bulgaria.**
C26.9	Gastrointestinal stromal tumor	Epirubicin, Ondasetron, Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**2 orphan drugs are available in Bulgaria - Imatinib mesilate, EU designation date: 20/11/2001and Nilotinib hydrochloride monohydrate, marketing authorization date: 19/11/2007. One more orphan drug is designated but not available in Bulgaria.**
C34.9	Lung cancer, small cell	Mitomycin, Ondasetron, Granisetron, Palonosetron,Tropisetron,Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**2 orphan drugs are designated but not available in Bulgaria (Pleoplatin, EU designation date:06/12/2007 and Anthrubicin hudrochloride, EU designation date: 02/04/2008).**
C43	Melanoma, familial	Interferon alfa, Interferon alfa-2a, Ondasetron,Granisetron,Palonosetron,Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochlorid	**No orphan drugs are designated. Access to local treatment only.**
C45	Mesothelioma	Bleomycin, Ondasetron, Granisetron, Tropisetron, Pemetrexed, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**2 orphan drugs are designated but not available in Bulgaria (Ranpirnase, EU designation date: 29/03/2001 and NGR-human tumour necrosis factor, EU designation date: 03/06/2008).**
C56	Ovarian germ cell malignant tumor	Topotecan, Cisplatin, Bleomycin, Paclitaxel, Epirubicin, Ondasetron Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine HCl	**One orphan drug is available and reimbursed in Bulgaria - Paclitaxel, EU designation date:18/12/2006. Another 9 medicinal products received orphan designation but not available in Bulgaria.**
C61	Prostate cancer, familial	Bicalutamide, Flutamid7, Triptorelin,Goserelin, Leuprorelin, Buserelin, Ondasetron,Granisetron Palonosetron, Tropisetron, Cyproterone, Methylpred-nisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.**
C62	Teratoma	Bleomycin, Etoposide, Palonosetron Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.**
C64	Nephroblastoma, Perlman syndrome, Renal cell carcinoma, familial	Interferon alfa, Interferon alfa-2a, **Sorafenib**, Sunitinib, Bevacizumab, Ondasetron, Granisetron, Palonosetron, Tropisetron, Vincristine, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**1 orphan drug is available and reimbursed in Bulgaria - Sorafenib tosylate. Everolimus is orphan drug which is not reimbursed but available in Bulgaria. Temsirolimus is orphan drug, registered via the centralized procedure (marketing authorization date: 19/11/2007). 17 drugs are received orphan designation but are not available in Bulgaria**
C81	Hodgkin lymphoma, classical	Epirubicin, Bleomycin, Etoposide, Ondasetron Granisetron, Palonosetron,Tropisetron, Vincristine, Vinblastine. Carmustine, Lomustine, Methylpredni-solone, Tramadol, Dihydro codeine, Morphine,Fentanyl, Pethidine hydrochloride	**3 drugs received orphan designation but are not available in Bulgaria.**
C82	Follicular dendritic cell sarcoma	Ibritumomab tiuxetan, Rituximab, Ondasetron, Granisetron, Palonosetron,Tropisetron, Liposomal Cytarabine,Cladribine, Methyl-prednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.**
C83	Non-Hodgkin lymphoma	Rituximab, Ondasetron., Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**1 orphan drug is designated and available under the centralized procedure Cladribine (subcutaneous use), EU marketing authorization date: 14/04/2004. The drug is not reimbursed in Bulgaria.**
C84	Cutaneous lymphoma	Ondasetron, Granisetron, Palonosetron, Vinblastine	**2 orphan drugs are designated but not available in Bulgaria.**
C85.0	Dendritic cell sarcoma,Interdigitating dendritic cell sarcoma	Bleomycin, Ondasetron Granisetron,Palonosetron, Tropisetron, Vincristine, Vinblastine, Liposomal Cytarabine Methyl-prednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.**
C85.9	Lymphoma, primary pulmonary	Epirubicin, Etoposide, Ondasetron Granisetron,Palonosetron,Tropisetron, Vincristine, Fludarabine phosphate, Methyl-prednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**No orphan drugs are designated. Access to local treatment only.**
C90.0	Myeloma, multiple	Pamidronic acid, Interferon alfa, Interferon alfa-2a, Bortezomib, Ondasetron Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine HCl	**1 orphan drug is designated, available via the centralized procedure but not reimbursed (3-(4' amnioisoindoline-1'-one)-1-piperidine-2,6-dione, marketing authorization date: 14/06/2007). Another 4 drugs received orphan designation but not available in Bulgaria.**
C91.0	Leukemia, lymphoblastic, acute	Pegfilgrastim, Lenograstim, Filgrastim, **Dasatinib**, Ondasetron, Granisetron, Tropisetron, Vincristine, **Nelarabine**, Methylprednisolone , Tramadol, Dihydro codeine,Morphine, Fentanyl, Pethidine hydrochloride	**2 orphan drugs are available and reimbursed - Dasatinib, EU designation date:23/12/2005 and Nelarabine, marketing authorization date: 22/08/2007. Imatinib mesilate is available but not reimbursed in Bulgaria (EU designation date: 26/08/2005). Mercaptopurine received orphan designation in o4/2009 and is available but not reimbursed in Bulgaria. 4 orphan drugs are designated but not available in Bulgaria.**
C91.4	Leukemia, hairy cell;	Interferon alfa-2a, Interferon alfa-2a, Ondasetron, Palonosetron,Tropisetron, **Cladribine**, Methylpredni-solone, Tramadol, Dihydro codeine, Morphine,Fentanyl, Pethidine hydrochloride	**The orphan drug Cladribine is available and reimbursed. One more orphan drug is designated but not available.**
C92.1	Chronic myeloid leukemia,	Imatinib, Nilotinib, **Dasatinib**, Mitomycin, Ondasetron, Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine hydrochloride	**1 orphan drug is available and reimbursed (Dasatinib, EU marketing authorization date: 20/11/2006). Another 3 orphan drug are designated but not available in Bulgaria.**
C94	Leukemia, erythroid, acute	Idarubicin, Etoposide, Ondasetron, Granisetron, Palonosetron, Tropisetron, Methylprednisolone, Tramadol, Dihydro codeine, Morphine, Fentanyl, Pethidine HCl	**No orphan drugs are designated. Access to local treatment only.**
D56.1	Beta- thalassemia	**Deferasirox,** Deferiprone, Deferoxamine	**1 orphan drug is available and reimbursed – Deferasirox, 2 orphan drugs are designated but not available in Bulgaria.**
D66	Hemophilia	Coagulation factor VIII, Octocog alfa, Coagulation factor IX	**1 orphan drug is designated, available but not reimbursed (pegylated factor VIIa). 1 orphan drug is not available in BG**

Table 5. Rare diseases which are present in the Positive Drug List, annex 4 by the ICD code

ICD code	Rare disease name	Available reimbursed local treatment	Orphan drug availability and affordability
E22.0	Acromegaly, Acromegaly - cutis verticis gyrata - corneal leukoma	Pegvisomant	**Pegvisomant (marketing authorization date 13/12/2002) is reimbursed orphan drug.**
E74.2	Galactosemia, N-acetyl-alpha-D-galactosaminidase deficiency	Agalsidase beta, Laronidase, Alglucosidase alfa,	**No orphan drugs are designated.**
E84	Cystic fibrosis	Mulienzymes, Dornase alf	**3 orphan drug are available (Heparin sodium, EU designation date: 22/05/2006 and Levofloxacin EU designation date: 23/09/2008 and Mannitolum, EU designation date: 07/11/2005) but not reimbursed. 13 orphan drugs are designated but not available.**
I27.0	Pulmonary arterial hypertension	Iloprost, Sildenafil	**2 orphan drugs are available and reimbursed (Sildenafil citrate, marketing authorization date: 28/10/2005 and Iloprost, marketing authorization date: 16/09/2003). 3 other orphan drugs are available via centralized procedure but not reimbursed (Bosentan, marketing authorization date: 15/05/2002, Sitaxentan sodium, marketing authorization date: 10/08/2006 and Ambrisentan, marketing authorization date: 21/04/2008). Another 6 orphan products are designated but not available.**
P22.0	Acute respiratory distress syndrome, Infant, Hyaline-membrane-disease	Palivizumab	**One orphan drug is designated but not available (Sinapultide, EU designation date: 29/07/2004).**
Q96	Turner syndrome	Somatropin	**No orphan drug is designated.**

Conclusions

Although the Bulgarian legislation concerning rare disease and orphan drugs is harmonized with the EU policies, Bulgarian patients with rare diseases have access to very few of the orphan drugs authorized in EU and the majority of the drugs covered are intended for symptomatic and supportive treatment. Only several rare diseases could be treated with the reimbursed orphan drugs.
Orphan drugs are reimbursed for 10 rare diseases and other treatment is covered 100 % for another 28 diseases. For another 39 rare diseases there are partially reimbursed supportive and symptomatic treatment.