Access to affordable medicines for rare diseases

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Definition

No single, widely accepted definition for rare diseases

Definitions vary - some are based on the number of people living with the disease, while others include various factors, such as the existence of adequate treatments or the severity of the disease.

- May involve chronic illness, disability, and often premature death
- Often have no treatment or not very effective treatment
- Are frequently not diagnosed correctly
- Are often very complex
- Are often caused by changes in genes

Rare Diseases

A large group of diseases which are characterized by a low prevalence in the population.

They frequently are associated with problems in diagnosis and treatment.

Because of definitions that include reference to treatment availability, a lack of resources, and severity of the disease, the term *orphan disease* is used as a synonym for *rare disease*.

Only about 400 rare diseases have therapies and about 80% have a genetic component according to the Rare Genomics Institute.

Prevalence (number of people living with a disease at a given moment), rather than incidence (number of new diagnoses in a given year), is used to describe the impact of rare diseases.

A large fraction of RDs affect children (75%). It is a striking fact that as much as 30% die before their fifth birthday.

Challenges of RDs

Epidemiological challenge	• lack of registries on the epidemiology
Pharmacological challenge	• lack of multicenter controlled therapeutic studies
Organizational challenge	• lack of standardized referral of patients with RDs in Europe
Legal challenge	• lack of legal basis for cross border genetic diagnostics
Ethical challenge	there are different priorities in different European countries

Difficulties in reimbursement decisions

- Member states have different strategies for implementation of OMPs following central EU authorization.
- Local reimbursement agencies sometimes tend to attribute a special status to OMPs, in which reimbursement is granted, in spite of high prices and undemonstrated effectiveness.
- Other agencies ask for additional (cost-) effectiveness studies at a national level.
- At the time of marketing authorization, the European Medicines Agency (EMA) can deal with incomplete clinical evidence by granting conditional marketing authorization or marketing authorization under exceptional circumstances.

The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe

➢Different types of reimbursement recommendations for orphan drugs issued by European health technology assessment (HTA) agencies and the reimbursement status of these drugs in the corresponding countries.

➢Reimbursement of orphan drugs does not always correspond to the type of HTA recommendation.

➢Separate calculations are used for three sub-groups: ultra-orphan drugs, oncology orphan drugs and other (non-ultra, non-oncology) orphan drugs.

➢

While the highest rate of reimbursement is observed (unsurprisingly) among drugs with positive or conditional recommendation, a high rate of reimbursement (11 %) is also observed among ultra-orphan drugs that have never been assessed by any HTA agency.

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What is the present situation with RDs in Macedonia?

The challenges in the access and care for rare diseases are mostly expressed in low population countries with limited financial possibilities, that have the following characteristics:

- Very rare occurrence in the overall population
- Lack of relevant epidemiological data
- Lack of experience and interest of the health care professionals
- Huge expenses for treatment of a few of the diseases, mostly abroad
- Lack of legislation regarding rare diseases
- Separately planned budget funds for treatment
- The full picture and the consequences for the society are not known.

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What is the present situation with RDs in Macedonia?

Genetic tests for rare diseases at RCGEB

Beta thalassemia	Hemochromatosis	Hunter's syndrome
Alpha thalassemia	Fragile X syndrome	Cystinuria
Cystic fibrosis	Tuberous sclerosis	Phenylketonuria
Hemophilia A	Rett syndrome	Galactosemia
Hemophilia B	Campomelic dysplasia	Prelingual Deafness
Huntington's disease	Achondroplasia	Darier's syndrome
Spinal muscular atrophy	Hypochondroplasia	Swyer's syndrome
Muscular dystrophy	Inherited deafness	Gilbert's Syndrome
Friedriech's ataxia	Metatropic dysplasia	Fanconi anemia
Congenital muscular dystrophy	X-linked adrenoleukodystrophy	Familial breast and ovarian cancer
Arrhythmogenic right ventricular dysplasia	Carnitine palmitoyl transferase II deficiency	Inherited trombophillias
Kennedy's disease	Androgen insensitivity	Globozoospermia
Chromosomal aneuploidies	Chromosome microdeletion sy	Y chromosome deletions

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NGS at RCGEB

Illumina MiSeq Personal Sequencer

- Targeted resequencing
  - Inherited Diseases (552 genes)
  - Inherited Cancer Panel (94 genes & 284 SNPs)
  - Tumor panel (somatic mutations in 26 genes)
  - Cardiomyopathy (46 genes)
- Clinical Exome Sequencing (4800 genes)

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The Obligations of the National Rare Disease Committee:

- ✓ Evaluation of eligible individual patents' dossier for inclusion in the rare disease registry;
- ✓ Inclusion of the eligible patients in the rare disease registry and individualizing their treatment;
- ✓ Deciding the list of drugs and quantities of drugs per year for treatment of the patients included in the registry;
- ✓ Preparation of a National strategy with an action plan for treatment of the patients with rare diseases, as well as additional strategic documents, protocols and treatment procedures.

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Official data from The Republic of Macedonia obtained from the registry of the patients with rare diseases

2018

- 406 patients with rare diseases in The Republic of Macedonia
- 135 patients were treated in 2018, with the obtained budget of 6 000 000 Euros (€)

2019

Planned finances for 2019, for the treatment of patients with diagnosed rare diseases in The R. Macedonia: 8 943 000 Eur (550 000 000 MKD)

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Drugs approved by the committee for treatment of rare diseases in The Republic of Macedonia

	ATC	Generic name	Form	Disease	Quantities per year	Euros (€)
1	A16AB02	imiglucerase	400 IE	Gaucher disease	1,050	1,348,780.49
2	A16AB09	idursulfase	6mg/3ml	Mucopolysaccharidosis II	270	693,198.79
3	B06AC04	Conestat alfa	2100 IE	Hereditary angioedema	900	678,824.49
4	A16AB12	elosulfase alfa	5mg/5ml	Mucopolysaccharidosis IV	768	600,679.65
5	B06AC01	human C1-esterase inhibitor	500 IE	Hereditary angioedema	930	595,538.147
6	L01XE18	ruxolitinib	5mg	Myelofibrosis	12,992	399,464.92
7	N07XX08	tafamidis	20mg	Familial amyloid polyneuropathy	990	321,414.69
8	A16AB11	taliglucerase alfa	200IE	Gaucher disease	480	279,500.49
9	B02BD07	Coagulation factor XIII	250 IU	Prophylactic treatment of congenital factor XIII deficiency	804	140,707.84
10	A16AX07	sapropterin	100mg	Hyper-phenylalaninaemia	5,200	109,670.11
11	V03AC03	deferasirox	500mg	Chronic iron overload syndrome caused by a genetic blood disorder in adults and children who are at least 10 years old	4,340	80,592.04
12	B02BX05	eltrombopag	50mg	Idiopathic thrombocytopenic purpura	728	42,871.03
13	M01CC01	penicillamine	250mg	Wilson	29,000	37,393.50

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Drugs approved by the committee for treatment of rare diseases in The Republic of Macedonia in 2018

	ATC	Generic name	Form	Desease	Quantities per year	Euros (€)
14	C02KX01	bosentan	125mg	Pulmonary arterial hypertension	1,456	35,546.76
15	L04AC07	Tocilizumab	200mg / 10ml	Chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) in patients two years and older	118	35,331.77
16	A16AX04	nitisinone	5mg	Tyrosinemia type 1	1,020	25,543.12
17	A16AX06	Miglustat	100mg	Niemann-Pick disease, type C .	504	23,803.22
18	G04BE03	Sildenafil	20 mg	Pulmonary arterial hypertension	5,400	17,183.41
19	N07XX06	tetrabenazine	25mg	Symptomatic treatment of hyperkinetic movement disorders	4,032	8,853.35
20	N07XX02	Riluzole	50mg	Amyotrophic Lateral Sclerosis	2,520	5,385.01
21	G04BE03	Sildenafil	50mg	Pulmonary arterial hypertension	2,500	5,098.37
22	N03AX17	stiripentol	250mg	severe myoclonic epilepsy in infancy (Dravet syndrome)	1,800	4,873.17
23	H05AA02	teriparatide	20 mcg / 0,5 ml	Autoimmune hypoparathyroidism	33	1,750.00
24	N03AG04	vigabatrin	500mg	infantile spasms	1,710	1,196.44
Total EUROs (€)						**6,000,000.00**

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14	G04BE03	Sildenafil	50mg		2,500	5,098.37
						57,828.55

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Expenses for treatments of rare diseases in The Republic of Macedonia in 2018

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				Total EUROs (€)		**6,000,000.00**

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Conclusion

- Establishing a collaborative, multi-institutional research infrastructure, as a new and innovative approach which would help to expand and develop the adequate response for the needs of the rare diseases community.
- Forging a public–private partnership which could be important in bringing orphan treatments to the market.
- Developing an integrated national or international system for collaborative research in the domain of rare genetic disorders


Thank
you!