State of the Art of Rare Diseases – Activities in EU Member States and Other European Countries

Latvia Report

Definition of a Rare Disease

Latvia has adopted the European Commission definition of a rare diseases and the National Plan for rare diseases espouses this definition.

National Plan

The Latvian National Plan covered the years 2013 to 2015, currently a report is being prepared on its implementation and activities are being planned for 2017-2020.

The National Plan, once created, was adopted at the most senior level by the Ministry of Health.

Currently there is no associated funding to ensure long term sustainability of the measures within the national plan. Funding of the plans activities has been incorporated into the general budget. Costs related to rare diseases are currently included in the national health care budget. An example of this funding can be seen in the creation of the Cabinet of Cystic Fibrosis, funded by the state this centre is housed within the Children's Clinical University Hospital. Additionally in 2014 a programme was founded, "Rare Disease Medicine Treatment for Children", which was also funded by the State. State funding for this programme in 2014 was €1,302,702 and in 2015 the funding was increased to €1,990,076.

The Ministry of Health of the Republic of Latvia has designated The Centre for Disease Prevention and Control which is currently responsible for the collection of data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Latvia for entry into the Orphanet database. The Centre for Disease Prevention and Control is the supervising authority and keeper of the Register of Patients with particular diseases, including congenital anomalies. Since September 2014 the Centre has used Orphacoding within the Register of Patients for those patients with rare congenital anomalies.

There is no dedicated advisory body responsible for overseeing the drafting or implementation of the national plan however the Ministry of Health has monitored the activities of the plan, its implementation and it organised meetings on specific cases or problems which patient organisations were invited to attend.

In the Plan activities were included which required additional budget and during this period the Ministry of Health, in cooperation with different specialists and patient organisations, identified the current situation, sought to find solutions and were looking for solutions to it and of course nominate future priority activities. For example Latvia began to register patients and coding rare diseases on official registries. The new-born screening programme has been revised and the idea of an identify card for patients with rare diseases has been discussed. These are only some the activities which have been planned or implemented.

<u>Organisation of RD Health and Social Care</u>

Centres of Expertise

There are currently no official designated Centres of Expertise for rare diseases in Latvia. The Ministry of Health, Orphanet team and experts from 3 university hospitals have been working on the development of the national criteria for Centres of Expertise to be registered on the Orphanet database. However several medical centres, that fulfil this role, are currently recognised by reputation only. For example, the Children's Clinical University Hospital provides genetic services, as well as services for children with haematological, oncological and endocrinological diseases. Riga East Clinical University Hospital has a specialised clinical for chemotherapy and haematology, in which patients with haemophilia A and B, factor XII deficiency and von Willebrand disease receive diagnostics and treatment. Rare oncological diseases e.g. Burkitt's lymphoma, Langerhans cell histiocytosis, Mantle-cell non-Hodgkin's lymphoma, multiple endocrine neoplasia, Ewing's sarcoma, Wilms' tumour, Waldenstrom's macroglobulinaemia, and others can be treated in this hospital also. Pauls Stradins

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Clinical University Hospital provides services in different rare disease areas, such as cardiology, angiology, pulmonology, nephrology, endocrinology, gastroenterology, oncology and ophthalmology. Latvian Pulmonary Hypertensions Centre is part of the Centre of Cardiology of Latvian University located in Paul Stradins Clinical University Hospital.

Currently Latvia does not have national legislation governing the process of designating Centres of Expertise. However planned amendments to the law have been initiated that provide the Cabinet of Ministers the powers to determine the requirements of medical institutions (structural units of university hospitals or specialised hospitals) that wish voluntarily to join the European Reference Networks (ERNs) and the procedures by which the medical institutions join the European Reference Networks. Centres of Expertise must comply with the current existing minimum requirements for medical institutions, as defined by the Regulation of the Cabinet Ministers of the Republic of Latvia No.60 "Regulations regarding the Mandatory Requirements for Medical Treatment institutions and their structural units" which was adopted in January 2009. In addition with the requirements prescribed by the European Commission delegated decision 10 March 2014 setting up criteria and conditions that European Reference Networks and healthcare providers wishing to join a European Reference Network must fulfil (2014/286/EU).

European Reference Networks

At present one HCP is participating as a full member of two ERNs in Latvia.

Member	European Reference Networks (ERNs)
Children's Clinical University Hospital, Riga	ERN EYE ERN PaedCan

Rare Disease Registration

There are no specific regulations in place for registries for rare disease however there are regulations associated with the registration of patients with particular diseases including congenital anomalies, some of which are rare diseases. The Congenital anomalies register forms the basis of the rare disease register. The Centre for Disease Prevention and Control is the supervising authority and keeper of the Register of patients with particular diseases including congenital anomalies. Since September 2014 Orphacoding has been used for rare diseases in the register of patients with congenital anomalies. As of September 2016 there were 249 cases in the registry coded with Orphacoding.

Specialists from university hospital centres collect rare disease patient data, for example the Latvian Cardiology Centre hosts the Pulmonary Arterial Hypertensions patient's database.

Genetic Testing

According to the regulation Nr.1529 "Organizing and Financing Procedure for Health Services" (further – Regulation), introduced by the Cabinet of Ministers on December 17th 2013 genetic testing is state funded. Any laboratory, that has an agreement with Service and have appropriate technical resources, can perform genetic testing according to Regulation Nr.1529. Genetic testing is available in the Medical Genetics Clinic of Latvian State University Children Hospital, Molecular Laboratory, Riga Stradins University Scientific Laboratory and in Latvian Biomedical Centre of Research and Study Centre.

Genetic testing of rare diseases is possible in collaboration with scientific research laboratories within the scopes of research projects financed by scientific grants or scientific budget of institution.

The genetic testing of the following rare disorders in Latvia is available as a diagnostic test or on a research basis:

- MD1 (Myotonic dystrophy type 1)
- MD2 (Myotonic dystrophy type 2)
- Congenital Myotonia (CLCN1 gene frequent mutations)
- LGMD1C (Limb-girdle muscular dystrophy 1C)

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- LGMD2A (Limb-girdle muscular dystrophy 2A)
- LGMD2I (Limb-girdle muscular dystrophy 2I)
- LGMD2L (Limb-girdle muscular dystrophy 2L)
- SCA1 (Spinocerebellar ataxia type 1)
- SCA2 (Spinocerebellar ataxia type 2)
- SCA3 (Spinocerebellar ataxia type 3)
- SCA6 (Spinocerebellar ataxia type 6)
- Rett syndrome
- MEN2A (multiple endocrine neoplasia)
- PKU (Phenylketonuria) MCADD (ACADM gene K329E mutation) LCHADD (HADHA gene 1528G>C mutation) Fragile X syndrome
- Nonsyndromic hearing loss (GJB2 gene) Spinal muscular atrophy (SMN1 gene) Prader Willi syndrome (SNRPN gene methylation statuss) Huntington disease (HTT gene) 3
- Central core disease (RYR1) Charcot-Marie-Tooth disease (PMP22 gene)
- Von Hippel-Lindau disease (VHL gene)
- PTEN gene associated syndromes
- APC-associated polyposis conditions
- RET gene associated syndromes
- Lynch syndrome
- Li-Fraumeni syndrome
- Arrhythmogenic right ventricular cardiomyopathy
- Ornithine transcarbamylase deficiency
- Hereditary pancreatitis
- Cystic fibrosis
- Wilson disease
- α1-antitrypsin deficiency, A1AD

In addition here are links to Regulation Nr.1529 and Regulation Nr.611 governing the use of genetic testing: http://likumi.lv/doc.php?id=263457 and http://likumi.lv/doc.php?id=140695.

Genetic testing can be provided in other EU and EFTA states with an S2 form. If genetic testing is for the purposes of healthcare and cannot be provided in the Republic of Latvia, it can be financed via the state budget.

Neonatal Screening

Neonatal screening is provided in accordance with Regulation Nr.611 which concerns the “Delivery care providing procedure” introduced by the Cabinet of Ministers as of July 2006. Data regarding screened new-born children within maternity units is collected in the New-borns Registry supervised by the Centre for Disease Prevention and Control. According to regulation Nr.611 tests within the neonatal screening programme include:

- Phenylketonuria
- Congenital hypothyroidism
- Hearing test

Clinical Practice Guidelines (CPGs)

In Latvia clinical guidelines for rare disease at the national level have not been approved. The Centre for Endocrinology of Pauls Stradins University Hospital in collaboration with Riga East University Hospital endocrinologists and Latvian State University Children's Hospital endocrinologists, issued in 2013 the "Diagnostic algorithms of rare endocrine diseases". These recommendations contain information of patients with a suspected endocrine disease in an organised and short form. The recommendations are aimed at helping general practitioners and endocrinologists to think about rare diseases when presented with certain types of patients.

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Training and Education

Every year the “Baltic metabolic specialist meeting” is held; in 2013 the meeting was held in Riga. The meetings bring together geneticists and laboratory specialists from Baltic countries. Pauls Stradins University hospital organises post-diploma educational courses for different specialists in most areas of medicine, endocrinology among them. The programme usually covers not only the most common clinical conditions but rare diseases also.

In addition, scientific literature was published in Latvia: "Rare diseases"(Professor A. Lejnieks, 2014,)"Porphyria. Myths, legends and reality (professor A.Lejnieks, 2015,) and "Recommendations for neuroendocrine tumour diagnosis, treatment and dynamic observation" (Professor A. Lejnieks, 2015

Activities of Orphanet/Alternative RD-specific information system

Latvia has an operational National Orphanet team which is hosted by the Centre of Disease Prevention and Control which is an institution partnered with RD-ACTION. The team produces information within the Latvian national language. The activities of the Orphanet team are funded only from the state budget within the framework of the RD-ACTION project as a national part of the co-funding of the project.

The team collects and enters data on rare disease related services into the Orphanet database. This information includes:

- Expert Centres – there are 6 centres in total
- Medical Laboratories – there are 2 laboratories and 21 diagnostic tests.
- Patient organisations – there are 4 patient organisations and a National Alliance of Patient organisations within Latvia.

The website dedicated to Orphanet in Latvia is regularly updated by the Orphanet team. The website was recently updated to include a section dedicated to useful information for patients, relatives and specialists. The following Information is available in Latvian:

- A video about the symptoms of Porphyria
- A family guide to SMA
- A DMD family guide
- A CMD family guide
- European recommendations for the primary prevention of congenital anomalies.

Helplines

There is no helpline in place dedicated to rare diseases within Latvia. However there is a helpline for children with rare diseases which aims to provide access to healthcare support as a priority. The service is coordinated by a paediatrician with competence in rare disease. The access is offered during office hours from The Clinic of Medical Genetics and Prenatal Diagnostics at The Children’s University hospital.

Official Information Centres

There are no official or unofficial information centres for rare diseases in Latvia.

<u>Rare Disease Research Activities</u>

Existence of RD Research programmes/projects

There are no specific programmes or projects in place which fund or facilitate rare disease research in Latvia. Funding is available for rare disease projects through the State budget, charities and pharmaceutical companies although funds are not specifically earmarked for rare disease research and rare diseases have not been highlighted as a priority direction for science or research in Latvia. Local activities are organised by University hospitals. Pauls Stradins University Hospital collaborated with the Latvian Biomedical Centre of

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Research and Studies to perform research into rare endocrine diseases. This collaboration included the genotyping of family members for specific mutations, genetic counselling and the search for genetic markers.

Participation in E-rare and International Research Initiatives

Latvia is an observer of the E-Rare Project. (http://www.erare.eu/)

National Alliance of Patient Organisations and Patient Representation

In Latvia, a national alliance of rare disease patient organisations has existed since 2014. These organisations, such as the Haemophilia Society, Pulmonary Hypertension Associations, Cystic Fibrosis Society, Association of People with Special Needs "Motus Vita" and "Caladrius". These organisations often collaborate with each other and work to organise events to celebrate Rare Disease Day each year. The alliance represents a specific group of rare diseases at a national level.

Integration of rare diseases into social policies and services

Specific actions exist to enable real access for people rare diseases to general social/disability programmes. These include training and guidelines for social workers. Respite care services are available and the categories of patients who are eligible for reimbursement are described in the Regulation Nr.1529. Therapeutic recreational programmes are also available and costs are included in the national health care budget. There are existing government-run services promoting social integration of those with handicaps into the school environment and workplace.

Individual care plans including access to social care and support services are available. As of January 2013 a new service for persons with disabilities (including persons with disabilities as a result of a rare disease) was launched. A municipality based service provides individuals with assistance when performing activities outside of the home; for example helping a person to travel to their place of work or learning or to attend a rehabilitation institution for therapy. Those eligible for the service are:

- Persons deemed to be have a disability Group I or Group II, categories which are based upon the conclusions drawn from the Stated Medical Commissions for the Assessment of Health Conditions and Working Ability on the necessity for a service of an assistant;
- Persons with a disability aged between 5 and 18 years of age, on the basis of conclusions made by the Stated Medical Commission for the Assessment of the Health Condition and Working Ability on the necessity for special care due to severe functional impairments.

The service of an assistant amounts to 40 hours a week within the territory of Latvia, except for persons within Group I visual disability who receive a benefit for using the services of an assistant for 10 hours per week and who receive a service of up to 30 hours a week if the services of an assistant exceed 10 hours per week. These exceptions are specified by the municipality Social Service Office.

Currently there are no specific measures in place to support the integration of rare disease specificities into the national system responsible for assessing a person's level of functioning. Patients with rare diseases receive the same support as the other patients, according to their needs.

Orphan Medicinal Products

Since 2009 some OMPs for children have been available as part of a special programme known as "Medical Treatment of Rare Disease for Children". The programme, which take place at the Children's University Hospital, in Riga OMPs such as Mecaserminum (Increlex), Sapropterini dihydrochloridum (Kuvan), Betaine anhydrous (Cystadane), Everolimusum (Votubia) are provided.

Orphan medicinal products are partially available via the reimbursement system. Dasatinibum (Sprycel), Nilotinibum (Tasigna), Plerixaforum (Mozobil), Romiplostimum (Nplate) are included in the positive reimbursement list. 2% of reimbursement budget is intended to individual reimbursement with limitation up to 14 228, 72 euro/ year for a single patient.

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Within this individual reimbursement, the following orphan medicinal products are provided: Ambrisentanum (Volibris), Nintedanibum (Ofev), Deferasiroxum (Rxjade), Stiripentolum (Diacomit), Olaparibum (Lynparza), Icatibantum (Firazyr), Sorafenibum (Nexavar), Pirifenidonum Esbriet), Eculizumabum (Soliris).

The following 29 EU orphan medicinal products were placed on the market during the period from January, 2015 till June, 2016:

- Adcetris,
- Cystadane,
- Deltyba,
- Diacomit,
- Elaprase,
- Esbriet,
- Evoltra,
- Exjade,
- Gazyvaro,
- Gliolan,
- Imbruvica,
- INCRELEX,
- Kuvan,
- Lynparza,
- Mozobil,
- Myozyme,
- Nexavar,
- Nplate,
- Ofev,
- Peyona,
- Revlimid,
- SIRTURO,
- Soliris,
- Sprycel,
- Tasigna,
- TOBI Podhaler,
- Volibris,
- Votubia,
- Yondelis.

The maximum retail prices of the medicinal products outside the reimbursement system are available on the State Agencies of Medicines website (www.zva.gov.lv).

There are measures in place to facilitate access to OMPs for patients, an applicant for a European Marketing Authorisation or clinical trial sponsor can request a permit to distribute a medicinal product which does not yet have a marketing authorisation for compassionate use based on substantial requests from medical institutions. There is a procedure to govern the application and distribution of such medicinal products which is provided in Regulations No 416 of the Cabinet of the Minister of Latvia “Procedure of Distribution and Quality Control of Medicinal Products” which was adopted in June 2007.

Rare diseases are treated not only with medicinal products designated as orphan drugs. There are therefore no specific provisions for pricing of orphan drugs, and they are subject to general pricing and reimbursement rules.

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Rare Disease Day

Every year patient organisation arrange the events which are held on Rare Disease Day in Latvia. There are activities which take place in The Children's University Hospital in the "Months for the Rare Diseases". Events have included:

- In March a photo exhibition, housed in The Children's University Hospital, opened for patients with rare diseases;
- An email address was unveiled (retasslimibas@bkus.lv) which provides users access to advice from a specialist.
- A press release was made in the public sphere regarding rare diseases in Latvia.
- The International Conference of Pulmonary Hypertension was held.
- The International Conference of Cystic Fibrosis in the Baltic States was organised.
- The Baltic States Paediatric Congress dedicated one of its sections exclusively to rare diseases.

Other

Latvia has accomplished much since 2014:

- A report has been written on the implementation of the National Plan and Latvia is currently in the process of planning the priorities of the new plan for rare diseases from 2017.
- Latvia has increased awareness and knowledge of rare diseases of medical staff, patients and the general public.

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