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2012 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE OF THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES

STATE OF THE ART OF RARE DISEASE ACTIVITIES IN THE NETHERLANDS

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More information on the European Union Committee of Experts on Rare Diseases can be found at www.eucerd.eu.

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ACRONYMS

General

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area (Iceland, Switzerland, Norway)
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

Pilot European Reference Networks

Dyscerne - European network of centres of expertise for dysmorphology
ECORN-CF - European centres of reference network for cystic fibrosis
Paediatric Hodgkin Lymphoma Network - Europe-wide organisation of quality controlled treatment
NEUROPED - European network of reference for rare paediatric neurological diseases
EUROHISTIONET - A reference network for Langerhans cell histiocytosis and associated syndrome in EU)
TAG - Together Against Genodermatoses – improving healthcare and social support for patients and families affected by severe genodermatoses
PAAIR - Patients' Association and Alpha-1 International Registry Network
EPNET - European Porphyria Network - providing better healthcare for patients and their families
EN-RBD -European Network of Rare Bleeding Disorders
CARE-NMD -Dissemination and Implementation of the Standards of Care for Duchenne Muscular Dystrophy in Europe project
ENERCA - European network for rare and congenital anaemia – Stage 3

GENERAL INTRODUCTION TO THE REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE OF THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES

The 2012 Report on the State of the Art of Rare Disease Activities in Europe was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2011. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of either the European Commission, its Agencies or national health authorities.

The report is split into five parts:

Part I: Overview of rare disease activities in Europe
Part II: Key developments in the field of rare diseases in 2011
Part III: European Commission activities in the field of rare diseases
Part IV: European Medicines Agency activities and other European activities in the field of rare diseases
Part V: Activities in EU Member States and other European countries in the field of rare diseases

Each part contains a description of the methodology, sources and validation process of the entire report, and concludes with a selected bibliography and list of persons having contributed to the report.

The present document contains the information from Parts II and V of the report concerning the Netherlands. A list of contributors to the report and selected sources are in annex of this document. For more information about the elaboration and validation procedure for the report, please refer to the general introduction of the main report[1].

[1] http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf

RARE DISEASE ACTIVITIES IN THE NETHERLANDS

Definition of a rare disease

Regulation (EC) 141/2000 on orphan medicinal products defines a rare disease: the prevalence of a rare disease is not higher than five per 10,000 individuals. The Netherlands will, for the time being, take no initiatives to amend the definition.

National plan/strategy for rare diseases and related actions

The Health insurance Act is at the basis of the Netherlands' health care system. All patients, including patients with a rare disease, are entitled to diagnosis, care and rehabilitation in line with this Act.

The Minister of Health, Welfare and Sport, Mrs. E. Schippers, sent a letter (with annex) to Parliament on 29 February 2012, in which she expounded the strategy of the Netherlands regarding rare diseases for the years 2012-2015[2]. Some important points in this report are the following:

- Strengthening the role of university hospitals with regard to patient care and research in rare diseases;
- Funding is designated for care and research;
- Improving reimbursement of orphan medicinal products applied in university hospitals starting 1 January 2012 and in the out-patient setting (starting some time in 3013, neither of the changes will jeopardise the accessibility of orphan medicinal products);
- A separate scientific programme is indicated (already started in 2011);
- The Steering Committee on Orphan Drugs was dissolved (as of 31 December 2011), but stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise;
- ZonMw (The Netherlands Organisation for Health Research and Development) assume tasks not taken up by the stakeholders that remain from the tasks of the former Steering Committee. The ministry of Health, Welfare and Sport provides additional funding for the years 2012-2015;
- The Forum Biotechnology and Genetics (also fully subsidised by the ministry of Health, Welfare and Sport) will assume more responsibility on rare diseases and orphan medicinal products;
- A statement on screening.

In addition to the national strategy initiated by the government for 2012-2015, preparations for a national plan on rare diseases for all stakeholders have started. The input of all stakeholders was collected via information from different meetings organised by several stakeholders in the last years and via newly installed working groups in 2011 and a new website and is coordinated by the Dutch Steering Committee on Orphan Drugs. This process will be continued in 2012 under the auspices of a sounding board especially formed for this task. On 1 October 2011 the site http://www.npzz.nl/ was launched in order to collect input for the national plan for rare diseases in a systematic way. The National Plan for Rare Diseases with input from all stakeholders is in an advanced stage of preparation, anticipated to be ready before summer 2012[3,4]. The national plan will consist of four chapters comprising the issues of information, care, research and availability of knowledge (education) and availability of therapy. However, within the purview of the Recommendation of the Council, the national plan will be incorporated into the national strategy. Stakeholders are, on the other hand, free to develop and implement initiatives on their own.

[2] An English language translation of the annex is under preparation.

[3] Following the adoption of the European Union Council Recommendation in June 2009, the Dutch government took no immediate initiatives to support a national plan/strategy for rare diseases. The reason being that there was already a 'strategy' in place since 2001 aimed at patients with rare disorders and at providing information about and accessibility of orphan drugs, embedded in wider governmental policies. This 'strategy' had a ten year time line. Nevertheless, the Steering Committee on Orphan Drugs along with the Dutch Genetic Alliance VSOP and the Forum Biotechnology and Genetics (FBG), lobbied for a national plan to be put on the political agenda, and both stated their intention at the 2010 Europlan National Conference on Rare Diseases to cooperate with stakeholders to prepare a national plan. Moreover, the Steering Committee on Orphan Drugs expressed their concerns about the preparation of a Dutch plan to the Minister of Health in December 2010.

[4] In a letter to the Minister of Health with a copy to Parliament, VSOP reacted rather critically on the ministers' strategy report, stating that she depicted the situation and governmental efforts too positively, leaving several real problems unaddressed, for example related to the lack of reference centres, the lack of a national registration, and the lack of standards of care.

Centres of expertise

All stakeholders – and also the government - support the idea that the (follow-up) care for patients with rare diseases should be concentrated in and/or coordinated from a limited number of centres, in order to guarantee expert care and to stimulate research. In order to stimulate the development of centres of expertise in the Netherlands the Steering Committee on Orphan Drugs developed criteria for expertise centres together with different stakeholders (hospitals, doctors, patients, researchers). These criteria are in line with the criteria established by the Rare Disease Task Force's working group on Standards of Care. The Dutch Federation of University Medical Centres started to make an inventory of existing expertise at national level in 2010 and the discussion on the definition of 'centres of expertise' has been initiated. Currently, the eight university medical centres in the Netherlands function as the main clinical reference centres for specific rare diseases. Other highly specialised care hospitals may also function as well-coordinated centres. However, only university hospitals are entitled to the reimbursement of clinically applied orphan medicinal products. The number of clinical reference centres for rare diseases varies considerably in the Netherlands, e.g. there are 13 government-appointed haemophilia centres, 6 centres for cystic fibrosis, 2 for MPS, and one each for Gaucher disease and Fabry disease. University medical centres provide genetic testing and counselling and run clinics in regional hospitals.[5].

Pilot European Reference Networks

The Netherlands participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUROHISTIONET, NEUROPED, Care-NMD and PAAIR (main partner).

Registries

There is no comprehensive national patient registry in the Netherlands, but several patient registries exist for specific rare diseases, including registries maintained by patient organisations and at the main clinical reference centres. The Dutch Orphan Disease Registry Consortium, established at the end of 2008, consists of several partners including four academic research groups, two pharmaceutical industry companies, three patient organisations, The Health Care Insurance Board and the Steering Committee on Orphan Drugs. This consortium aims to build an innovative, comprehensive, sustainable orphan disease registry framework that provides a practical and transparent approach to collect information on rare diseases, to encourage orphan medicinal product development and to optimise patient care. The group of rare inborn errors of metabolism, including lysosomal storage disorders, is used as the first model group of diseases to build such a registry framework. In this context the national web-based facilitating registry for inborn errors of metabolism has been developed further: the Dutch Diagnosis Metabolic Diseases Registry. The societal value of the DDRMD became obvious in 2010 as questions on the incidence of metabolic disorders from several interested parties can be answered now.

A registry of all patients referred with an abnormal neonatal screening result (NEORAH) has been put into place at the RIVM (National Institute for Public Health and the Environment). Furthermore, The Netherlands contributes to European registries including EIMD, TREAT-NMD, AIR, EUROCARE CF, EPCOT and EUROCAT.

Neonatal screening policy

On 1 January 2007, an extended neonatal screening program was launched in the Netherlands, for 18 rare disorders: phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis, biotinidase deficiency, galactosaemia, glutaric aciduria type I, HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, maple syrup urine disease, MCAD deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, sickle cell disease, tyrosinemia type I, longchain hydroxyacyl-CoA dehydrogenase deficiency and very-long-chain acyl-CoA dehydrogenase deficiency.

The Netherlands (RIVM, VUMC and VSOP) was involved in the EC project "Evaluation of population newborn screening practices for rare disorders in Member States of the European Union" funded by the EC/EAHP, that started in 2010. This project aimed at identifying and evaluating all aspects deemed relevant to the implementation of a public health action in neonatal screening resulting in a report on the practices of

[5] The Steering Committee on Orphan Drugs recommends the establishment of an independent body that will identify and periodically review the centres of expertise on the basis of the aforementioned criteria. This recommendation was forwarded to the Ministry of Health, Welfare and Sport. However, the Ministry will wait at least two years for results regarding the development of centres of expertise / reference centres for rare diseases in university hospitals.

neonatal screening for rare disorders implemented in all the Member States. This report was published in the beginning of 2012.

Thanks to developments in both therapy as well as screening methodologies, some of the lysosomal storage disorders may soon meet the criteria set by the Health Council of the Netherlands in 2005 for the national neonatal screening program. Most lysosomal diseases have a broad clinical spectrum and neonatal screening will probably not just identify patients who will develop symptoms within a few months after birth, but also persons who will develop symptoms at later age. The ethical, legal and societal aspects of neonatal screening for some lysosomal storage disorders are being investigated by two Dutch research groups.

Screening is not primarily oriented towards rare diseases, but aimed at those diseases for which some form of treatment is available. In other words establishing a diagnosis in a patient via screening should in theory lead to a gain in health.

Genetic testing

Genetics services in the Netherlands are funded by the health insurance through a special budget; services include genetic counselling, chromosome analysis, biochemical (enzyme) diagnostics and DNA-diagnostics. All 8 University medical centres are licensed for clinical genetics; to provide counselling and pre- and postnatal testing. Genetic counselling is offered locally or in out-clinics affiliated to the centre. All services are offered regionally except for the DNA-diagnostics which, since their start in 1988, operate at a national level. All genetic laboratories are accredited according to ISO 15189 (international standard for medical laboratories). Each DNA laboratory provides a specific package of gene tests, tests for the more frequent genetic disorders, like breast cancer are offered by more centres. Tests for rare disorders usually performed in one laboratory only. Expertise and research is leading in the portfolio of tests offered. Together the 8 Dutch laboratories for DNA-diagnostics offer tests for over 900 genes[6].

Diagnostic tests are reimbursed by health care insurance on the condition that there is a medical reason to do this test. For tests that are not available in the Netherlands, samples can be sent abroad. Molecular genetic laboratories have distributed the tests according to specific expertise that is available. Testing upon request without an indication (for instance preconception cystic fibrosis testing) was not available until the end of 2010[7].

National alliances of patient organisations and patient representation

The development of a national alliance of rare disease patient organisations is under discussion by stakeholders. VSOP[8] represents about 65 member patient organisations for rare and genetic conditions, thereby acting as the national alliance for these patient organisations in the Netherlands. Specify attention is given to perinatal care, biomedical research, prevention, standards of care, ethical and societal issues. Some more common disorders are also represented in the VSOP membership. VSOP has a focus on the specific problems of rare disorders and represents EURORDIS in the Netherlands, but where there are several other patient umbrella organisations are dealing with (more general) health interests of relevance to people with rare disorders, such as the general organisation of health care (NPCF) and issues in the field of income and social participation (CG-Raad). VSOP participates in the Health Council, the RIVM (prenatal and neonatal screening), Forum Biotechnology and Genetics, ZonMw programs for health research, and several other health and health research policy platforms and committees.

In 2012, the government decided to decrease the budget for patient organisations from 43 to 25 million Euro's per year in the period 2012-2015, resulting in a minimum exploitation subsidy of € 25,000 and a maximum of €35,000 for a disease-specific organisation per year (previously, the maximum was €125,000). The exploitation subsidy for VSOP will end per 2014, therefore making VSOP fully dependent on project acquisition and donations.

Sources of information on rare diseases and national help lines

Orphanet activities in the Netherlands

Since 2004, there is a dedicated Orphanet team in the Netherlands, currently hosted by the VU University Medical Centre, Amsterdam and the Leiden University Medical Centre. The Leiden University Medical Centre was designated by the Ministry of Health, Welfare and Sport in 2010 as the official Orphanet team for the Netherlands. This team is in charge of collecting data on rare disease related services (specialised clinics,

[6] A list is available on the website www.DNA-diagnostiek.nl.
[7] www.vumc.nl/cftest offers CF carrier testing for 150€
[8] www.vsop.nl

medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Netherlands[9] national website in Dutch which was launched in 2011.

A collaboration has been established with Erfocentrum - the Dutch National Genetic Resource and Information Centre - and Orphanet. Erfocentrum provides information about genetic diseases to the Dutch general public and for that purpose it has written Dutch abstracts for approximately 500 rare genetic diseases. All of these abstracts are validated by clinical geneticists and patient organisations. This collaboration allows Orphanet to use the Erfocentrum abstracts to provide information about rare diseases to the Dutch-speaking public. Hyperlinks, leading to the Erfocentrum website containing the Dutch abstracts, will be added to the disease-pages on Orphanet.

Official information centre for rare diseases

Until the end of 2011, the Steering Committee on Orphan Drugs functioned as an information centre for rare diseases and orphan medicinal products in the Netherlands. The secretariat of the Steering Committee answered various questions from pharmacists, medical specialists, patients and their families and pharmaceutical companies about rare diseases and orphan medicinal products. Furthermore, the Steering Committee had a signalling function in response to problems that are reported to the steering committee. Their website www.orphandrugs.nl provided general information.

As of 31 December 2011, the Steering Committee was disbanded by the government: however €880'000 was made available to ZonMw (the Netherlands Organisation for Health Research and Development) for the years 2012-2015 to install a secretariat for rare diseases and orphan medicinal products.

Help line

The most specialised and most used help line for rare disorders is the Erfocentrum ERFO line, providing information on genetic and rare diseases and pregnancy/reproduction related questions. Meldpunt (Information Desk from the Dutch Consumer and Patient Federation NPCF) is a more general health line for information concerning social services and health care insurance. However, for 'new' patients or parents, specific and reliable information may be still difficult to find, which will be addressed in the working out of the National Plan.

Other sources of information on rare diseases

The National Genetic Resource and Information Centre (Erfocentrum), founded by the VSOP, has both a board of representatives of patient organisations and medical professionals and hosts the national helpline for information on genetic issues and rare diseases. The website www.erfocentrum.nl contains a database of rare diseases with information for both lay-persons and professionals (www.erfelijkheid.nl). In addition, public information is available on genetic, biomedical and pregnancy related issues[10]. The Erfocentrum runs since 2010 a new website (www.erfelijkheidinbeeld.nl) which hosts all kinds of videos, DVDs, and presentations produced by patient organisations on phenotype and hereditary and/or congenital disorders. Using this new portal, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

The VSOP also functions as a centre providing expertise and advocacy for patient organisations for rare and genetic disease. The Royal Dutch Association of Pharmacists (KNMP) has developed in collaboration with the Steering Committee on Orphan Drugs the website www.farmanco.knmp.nl/weesgeneesmiddelen which publishes practical information on European registered orphan medicinal products, in particular for pharmacists but patients can also make use of it.

Information on neonatal screening is available from the National Institute for Public Health and the Environment[11], both for the general public, parents and physicians.

Information is also provided by the many Dutch patient organisations, pharmaceutical companies and the Federation of University Hospitals, etc.

[9] http://www.orpha.net/national/NL-NL/index/homepage/?lng=FR

[10] These sites provide further web based information: www.biomedisch.nl; www.zwangernu.nl; www.zwangerwijzer.nl; www.slikeerstfoliumzuur.nl; www.prenatalescreening.nl

[11] www.rivm.nl/pns/hielprik

Good practice guidelines

In 2011, VSOP finished 30 out of 33 treatment guidelines for general practitioners as part of the project 'The patient as an information carrier', carried out in close collaboration with the patient organisations and the Dutch College of General Practitioners (NHG). Funding was provided by a Dutch health insurance fund (Innovatiefonds) for the production of guidelines. VSOP also continued to work on 17 standards of care for rare disorders, 4 of which will be finished in 2012, the others will be finished by 2014. Major funding (in total nearly €3million) was provided by the Dutch government.

Training and education initiatives

At governmental level, training and education initiatives in the field of rare diseases are not foreseen, because these are the remit of universities and professional organisations The Boerhaave Committee (at Leiden University Medical Centre) organises the annual Princess Beatrix Fund Symposium on Neuromuscular Diseases for medical specialists and their assistants.

There is a growing interest has been observed in university students to follow a lecture or write a paper on rare diseases or orphan medicinal products.

Training for health care providers on prenatal and neonatal screening is organised at a regular basis by the National Institute for Public Health and the Environment. Documents used in training are available at the website[12].

In addition, a course on practical clinical, radiological and pathological diagnosis of skeletal tumours was organised by the European network of excellence EuroBoNeT in collaboration with Leiden University Medical Center (14-16 February 2011).

National rare disease events in 2011

The Dutch Rare Disease Day 2011 was held on 15 May 2011[13] in Artis ZOO, Amsterdam, in conjunction, with the EURORDIS Conference. About 350 people, especially families, attended this meeting and two so called angel awards were granted for excellence in patient advocacy and medical care for rare diseases. This day was organised by the Dutch Steering Committee on Orphan Drugs, the Dutch Rare Disease Fund, the Pharmacists Association KNMP and VSOP. On 12 May 2011 a conference was organised by the Dutch member organisations of EURORDIS in collaboration with the Dutch Steering Committee on Orphan Drugs on care for rare diseases.

On 25 February 2011 the Patient Platform Rare Diseases organised a hearing event on rare diseases in the Dutch Senate in The Hague.

Hosted rare disease events in 2011

In 2011 the following rare disease related events were hosted by the Netherlands and reported in *OrphaNews Europe*: Optimal Role of Patient Organisations in Drug Development (24 March 2011, Amsterdam), 11th International Congress of the European Society of Magnetic Resonance in Neuropediatrics (24-26 March 2011, Amsterdam), The Third Birt-Hogg-Dubé Symposium (11-12 May 2011, Maastricht), Membership Meeting of EURORDIS, Amsterdam (13-14 May 2011), European Society of Human Genetics Conference, Amsterdam (28-31 May 2011).

Research activities and E-Rare partnership[14]

National research activities

A multi-annual research programme started in 2011 at The Netherlands Organisation for Health Research and Development (ZonMw) with a funding of 13.4€ million. The main objective of this is to stimulate translational research in rare diseases with the aim of developing therapies. For the programme €13.6 million is available. The first call was launched in early 2011. ZonMw has also provided and continues to provide funding through several research programmes for research on rare diseases (e.g. the Innovative Research Incentives Scheme, the Gene Therapy subsidy scheme and the additional research programme on efficiency of Expensive and Orphan Medicines).

There are tax reductions for R&D in high-tech start-ups from which orphan medicinal product companies can benefit. There are also several programmes from the Ministry of Economic Affairs to facilitate

[12] For instance information for screeners and information on the diseases screened: www.rivm.nl/pns/hielprik/films.

[13] www.zeldzameziektendag.nl

[14] This section has been written using the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp53-62).

start-ups (Innovation Subsidy Collaboration projects (IS), Subsidy programme on exploiting knowledge and Technostarters) that orphan medicinal product companies can benefit from.

In 2011, the Netherlands Organisation for Scientific Research made €22.5 million available to a consortium including 8 Dutch university medical centres and other research institutes and universities in order to establish a national biobanking infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure Netherlands (BBMRI-NL), which will integrate clinical materials and data gathered over many years with the goal of improving access to human samples. Such samples are important to rare disease and orphan medicinal product research. However for practical and cost-effectiveness reasons the infrastructure currently can only accept rare disease samples when they are part of biobanks of 1000 samples or more, so the infrastructure for now mostly concerns, rare diseases samples when they are part of a biobank for a more common disorder [15].

Participation in European research projects

The Netherlands participates, or has participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BIGHEART, BIONMD, CARDIOGENET, CHEARTED, BIOMALPAR, BNE, CELL-PID, CONTICANET, CURE-FXS, CRUMBS IN SIGHT, ELA2-CN, DIALOK, EDAR, EMVDA, EMINA, EUCLYD, EuPAPNet, EURO-CGD, EUMITOCOMBAT, EUNEFRON, EUROBONET, EURAMY, EUROCARE-CF, EUROGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, EVI-GENORET, EURODSD, EUROPADNET, EUROSTEC, HSCR, GENESKIN, GEN2PHEN, GENTECH, GENCODYS, GRIP, HDLOMICS, IMMUNOPRION, MLC-TEAM, NEMMYOP, NSEuroNet, NEUROSIS, NMD-CHIP, NOVSEC-TB, MITOCIRCLE, MITOTARGET, MMR-RELATED CANCER, MYASTAID, NEUROPRION, OLIGOCOLOR, PEROXISOMES, PERSIST, PNSEURONET, PRIBOMAL, PWS, TB-DRUG, TREAT-NMD, VACCINES4TB, VITAL, RD PLATFORM, and REVERTANT-EB.

E-Rare

The Dutch Organisation for Health Research and Development (ZonMw) and the Dutch Steering Committee Orphan Drugs participates in E-Rare 1 (2006-2010) and E-Rare 2 (2010-2014), and participated in the 2nd Joint Transnational Call in 2009 (€1.7 million was granted in funds for 14 Dutch research groups, involved in 9 of the 16 funded projects/consortia). The Netherlands did not participate in the 3rd E-Rare Joint Transnational Call (2011) but will participate in the 4th focused Joint Transnational Call (2012).

IRDiRC

The Netherlands Organisation for Health Research and Development (ZonMw) and the pharmaceutical enterprise Prosensa, are committed members of the IRDiRC.

Orphan medicinal products[16,17]

Orphan medicinal product committee

The Steering Committee on Orphan Drugs (Stuurgroep WGM) was established in 2001 by the Minister of Health: its mission was to encourage the development of orphan medicinal products and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases. This committee was an independent organisation and the members are representatives of umbrella

[15] Another interesting example is the following: VU University Medical Centre in Amsterdam is working together with the Dutch Neuromuscular Diseases Association in the development of an n-of-1 trial service. In the case of chronic conditions and fast-acting medicines for symptomatic treatment, it might be justified to collect evidence of efficacy from a trial treatment of a single patient. A "n of 1" is a clinical trial involving a single patient, i.e., a single case study. Through this service, patients with rare diseases would be able to receive treatment while at the same time testing the effectiveness of certain (expensive) medicines. During such an "n-of-1 trial" the physician alternately treats the patient with the off-label medicine and the medicine with which it is compared, for example, a placebo or treatment-as-usual. Rules are agreed in advance to allow for a fair comparison. The results of the trial treatment indicate whether the patient experiences benefits of the off-label medicine over and above treatment-as-usual. As series of trial treatments together bring more knowledge, these separate n-of-1 trials would be centrally coordinated and combined for analysis by an n-of-1 trial service. The current project is investigating whether such trial treatments, to be facilitated by the n-of-1 trial service, could be reimbursed by the Dutch basic health insurance. It is also examining whether the results of this type of research may be sufficient for authorities to decide on the effectiveness of an off-label medicine and its reimbursement for future patients with the rare disease in question. In a follow-up project, researchers hope to actually invite patients to participate in pilot trial treatments for neuromuscular diseases and eventually other diseases as well.

[16] This section has been written *using KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp53-62)

[17] *This section was written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp21-23)

organisations for patients and for pharmaceutical companies, physicians, a pharmacist, a representative of the Dutch medicine evaluation board a representative of the Dutch health insurance board. The Steering Committee was involved in the EC projects E-Rare, Europlan and Polka. The action plan for this committee from 2008-2011 covered three priority areas: 1) improved access to health care and treatment through centres of expertise, 2) the stimulation of research and development of Orphan medicinal products, 3) the creation of a sustainable reimbursement system. The budget of this committee was €450,000 per year. In 2011 the Steering Committee focused on the draft for a national plan in close cooperation with different stakeholders. However, it was decided that the Steering Committee would not be funded by the Dutch government after December 2011 and will no longer exist as a governmental committee from 2012 onwards. Stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise in the future with the Netherlands Organisation for Health Research and Development ZonMw taking more responsibility (with extra funding) and assuming a number of tasks from the former Steering Committee. Notably, the coordination of the development and implementation of a national strategy will be from 2012 onwards assumed by a secretariat at ZonMw.

Orphan medicinal product incentives

A waiver can be granted for the registration fee of a medicinal product if the medicinal product is already registered in one or several other EU member states and if the prevalence of the indicated disease is less than 1 in 200.000 inhabitants in the Netherlands.

Free advice was available from the Dutch Steering Committee on Orphan Drugs until the end of 2011. In the case of orphan medicinal products for a rare disease for which no alternative treatments exist, there is no obligation for companies to provide pharmaco-economic data. In individual cases this may also be the case for orphan medicinal products for a disease with a prevalence no more than 5 persons per 10,000 for which an alternative treatment does exist.

The programme for Expensive and Orphan Medicines (2007-2014) aims to investigate the effectiveness of expensive drugs and of expensive orphan medicinal products and the development of HTA methodology to help the Dutch Health Care Insurance Board in its advice on reimbursement. In the scope of this programme, several projects on registered orphan medicinal products have already been selected.

As of 1 January 2009, the subsidy scheme Orphan Designation Dossier (ODD) is in action. This is an initiative of the Dutch Steering Committee on Orphan Drugs and is executed by the Netherlands Organisation for Health Research and Development (ZonMw). This initiative will help stimulate the development of orphan medicinal products in the Netherlands by providing Dutch pharmaceutical Small and Medium-sized Enterprises (SMEs) a small subsidy for the costs of writing and submitting the ODD to the EMA. Analysis has shown that pharmaceutical SMEs are the engine behind orphan medicinal product development. The scheme will continue up to November 2016 with a total budget of €150,000. The scheme consists of two types of applicants – SME with ODD experience and SME without experience – and two types of subsidy – €7,200 and €3,600. Depending on their ODD experience, SMEs are allocated the large or small subsidy, provided their proposal meets all the formal criteria. A maximum of two ODD-support applications are permitted per SME per year. Five grants have been awarded at the end of 2011.

Orphan medicinal product market availability situation

In the Netherlands, all orphan medicinal products with EU market authorisation are available on the market.

Orphan medicinal product pricing policy

The pricing policy of orphan or non-orphan medicinal products is similar.

Orphan medicinal product reimbursement policy

In the Netherlands the following orphan medicinal products are reimbursed: Aldurazyme, Arzerra, Carbaglu, Cayston, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Firdapse, Glivec, Increlex, Kuvan, Lysodren, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Prialt, Replagal, Revatio, Revlimid, Revolade, Siklos, Soliris, Somavert, Sprycel, Tasigna, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Yondelis, Zavesca.

The following orphan medicinal products are available when ordered by a physician or a pharmacist either through a hospital budget or on a named-patient basis: Atriance, Busilvex, Ceplene, Esbriet, Firazyr, Gliolan, Inovelon, Litak, Mepact, Mozobil, Pedea, Photobarr, Peyona, Plenadren, Rilonacept Regeneron, Savene, Tepadina, Thalidomide, TobiPodhaler, Trisenox, Votubia, VPRIV and Vyndaquel.

For the use of orphan medicinal products in university hospitals, a reimbursement method *("beleidsregel weesgeneesmiddelen")* was introduced from 1 January 2006, to increase the use of orphan

medicinal products for treating rare diseases. The costs of the orphan medicinal products in university hospitals, in case they are accepted under this specific regulation, are totally refunded for a maximum of four years. In this period of temporarily refunding more information has to be collected on the efficiency of the product. After four years a re-evaluation takes place and the product may be listed permanently on the "beleidsregel weesgeneesmiddelen". For orphan medicinal products used outside the hospital (at home) there is a special reimbursement rule at the Medical Reimbursement System (GVS). Reimbursement can be asked for at the Health Care Insurance Board in case of off-label use in less than 1:150,000 inhabitants (i.e. less than 110 patients in the Netherlands). If a patient is chronically ill, they can request a personal budget (PGB) to obtain home care.

Other initiatives to improve access to orphan medicinal products

A physician may prescribe non-authorised drugs (e.g. drugs, including orphan medicinal products, authorized elsewhere or even not authorised anywhere), but only with an approval of the Health Inspectorate. The prescribed drug is not reimbursed, unless the health insurer chooses to do so. Apart from these provisions, there are no other initiatives regarding access.

Orphan devices

There are no initiatives regarding orphan devices.

Specialised social services

Respite care services are available, however not structurally imbedded in the general health care system. Organising respite services is left to private initiative, with or without funding from a health insurer. The personal budget (PGB) for patients who are dependent on non-medical care (due to disease, old age or handicap) can also be employed for respite care.[18] These services are Respite services include in-home respite, emergency respite, sitter-companion services, and therapeutic day care. A specialised nursing home for those with Huntington disease is run by the Health Insurance. Other therapeutic recreational services are provided by patient organisations, such as holiday homes for those with ataxia and neuromuscular diseases and camping car rental for Duchenne patients: patients may be asked to participate in the payment of such services. Social support, supported employment and support in travelling are available in order to help the integration of patients in daily life.

DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2011 IN THE NETHERLANDS

National plan/strategy for rare diseases and related actions

The Minister of Health, Welfare and Sport, Mrs. E. Schippers, sent a letter (with annex) to Parliament on 29 February 2012, in which she expounded the strategy of the Netherlands regarding rare diseases for the years 2012-2015[19]. Some important points in this report are the following:

- Strengthening the role of university hospitals with regard to patient care and research in rare diseases;
- Funding is designated for care and research;
- Improving reimbursement of orphan medicinal products applied in university hospitals starting 1 January 2012 and in the out-patient setting (starting some time in 3013, neither of the changes will jeopardise the accessibility of orphan medicinal products);
- A separate scientific programme is indicated (already started in 2011);

[18] However, certain changes were made in the PGB as of 2012 that will make funding of respite care more difficult.

[19] An English language translation of the annex is under preparation.

- The Steering Committee on Orphan Drugs was dissolved (as of 31 December 2011), but stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise;
- ZonMw (The Netherlands Organisation for Health Research and Development) assume tasks not taken up by the stakeholders that remain from the tasks of the former Steering Committee. The ministry of Health, Welfare and Sport provides additional funding for the years 2012-2015;
- The Forum Biotechnology and Genetics (also fully subsidised by the ministry of Health, Welfare and Sport) will assume more responsibility on rare diseases and orphan medicinal products;
- A statement on screening.

In addition to the national strategy initiated by the government for 2012-2015, preparations for a national plan on rare diseases for all stakeholders have started. The input of all stakeholders was collected via information from different meetings organised by several stakeholders in the last years and via newly installed working groups in 2011 and a new website and is coordinated by the Dutch Steering Committee on Orphan drugs. This process will be continued in 2012 under the auspices of a sounding board especially formed for this task. On 1 October 2011 the site http://www.nationaalplan.nl/ was launched in order to collect input for the national plan for rare diseases in a systematic way. The National Plan for Rare Diseases with input from all stakeholders is in an advanced stage of preparation, anticipated to be ready before summer 2012[20,21]. The national plan will consist of four chapters comprising the issues of information, care, research and availability of knowledge (education) and availability of therapy. However, within the purview of the Recommendation of the Council, the national plan will be incorporated into the national strategy. Stakeholders are, on the other hand, free to develop and implement initiatives on their own.

Sources of information on rare diseases and national help lines

Orphanet activities in the Netherlands

In 2011, the Orphanet Netherlands national website was launched in Dutch by the Orphanet Netherlands team[22].

Official information centre for rare diseases

Until the end of 2011, the Steering Committee on Orphan Drugs functioned as an information centre for rare diseases and orphan medicinal products in the Netherlands. The secretariat of the Steering Committee answered various questions from pharmacists, medical specialists, patients and their families and pharmaceutical companies about rare diseases and orphan medicinal products. Furthermore, the Steering Committee had a signaling function in response to problems that are reported to the steering committee. Their website www.orphandrugs.nl provided general information.

As of 31 December 2011, the Steering Committee was disbanded by the government: however €880'000 was made available to ZonMw (the Netherlands Organisation for Health Research and Development) for the years 2012-2015 to install a secretariat for rare diseases and orphan medicinal products.

Good practice guidelines

Funding was provided by a Dutch health insurance fund (Innovatiefonds) for the development of guidelines. VSOP also continued to work on 17 standards of care for rare disorders, 4 of which will be finished in 2012, the others will be finished by 2014. Major funding (in total nearly €3million) was provided by the Dutch government.

[20] Following the adoption of the European Union Council Recommendation in June 2009, the Dutch government took no immediate initiatives to support a national plan/strategy for rare diseases. The reason being that there was already a 'strategy' in place since 2001 aimed at patients with rare disorders and at providing information about and accessibility of orphan drugs, embedded in wider governmental policies. This 'strategy' had a ten year time line. Nevertheless, the Steering Committee on Orphan Drugs along with the Dutch Genetic Alliance VSOP and the Forum Biotechnology and Genetics (FBG), lobbied for a national plan to be put on the political agenda, and both stated their intention at the 2010 Europlan National Conference on Rare Diseases to cooperate with stakeholders to prepare a national plan. Moreover, the Steering Committee on Orphan Drugs expressed their concerns about the preparation of a Dutch plan to the Minister of Health in December 2010.

[21] In a letter to the Minister of Health with a copy to Parliament, VSOP reacted rather critically on the ministers' strategy report, stating that she depicted the situation and governmental efforts too positively, leaving several real problems unaddressed, for example related to the lack of reference centres, the lack of a national registration, and the lack of standards of care.

[22] http://www.orpha.net/national/NL-NL/index/homepage/?lng=FR

Training and education initiatives

A course on practical clinical, radiological and pathological diagnosis of skeletal tumours was organised by the European network of excellence EuroBoNeT in collaboration with Leiden University Medical Center (14-16 February 2011).

National rare disease events in 2011

The Dutch Rare Disease Day 2011 was held on 15 May 2011[23] in Artis ZOO, Amsterdam, in conjunction, with the EURORDIS Conference. About 350 people, especially families, attended this meeting and two so called angel awards were granted for excellence in patient advocacy and medical care for rare diseases. This day was organised by the Dutch Steering Committee on Orphan Drugs, the Dutch Rare Disease Fund, the Pharmacists Association KNMP and VSOP. On 12 May 2011 a conference was organised by the Dutch member organisations of EURORDIS in collaboration with the Dutch Steering Committee on Orphan Drugs on care for rare diseases.

On 25 February 2011 the Patient Platform Rare Diseases organised a hearing event on rare diseases in the Dutch Senate in The Hague.

Research activities and E-Rare partnership[24]

National research activities

A multi-annual research programme started in 2011 at The Netherlands Organisation for Health Research and Development (ZonMw) with a funding of 13.4€ million. The main objective of this is to stimulate translational research in rare diseases with the aim of developing therapies. For the programme €13.6 million is available. The first call was launched in early 2011. ZonMw has also provided and continues to provide funding through several research programmes for research on rare diseases (e.g. the Innovative Research Incentives Scheme, the Gene Therapy subsidy scheme and the additional research programme on efficiency of Expensive and Orphan Medicines).

In 2011, the Netherlands Organisation for Scientific Research made €22.5 million available to a consortium including 8 Dutch university medical centres and other research institutes and universities in order to establish a national biobanking infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure Netherlands (BBMRI-NL), which will integrate clinical materials and data gathered over many years with the goal of improving access to human samples. Such samples are important to rare disease and orphan medicinal product research. However for practical and cost-effectiveness reasons the infrastructure currently can only accept rare disease samples when they are part of biobanks of 1000 samples or more, so the infrastructure for now mostly concerns, rare diseases samples when they are part of a biobank for a more common disorder[25].

E-Rare

The Netherlands did not participate in the 3rd E-Rare Joint Transnational Call (2011) but will participate in the 4th focused Joint Transnational Call (2012).

[23] www.zeldzameziektendag.nl

[24] This section has been written using the KCE reports *112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp53-62).*

[25] Another interesting example is the following: VU University Medical Centre in Amsterdam is working together with the Dutch Neuromuscular Diseases Association in the development of an n-of-1 trial service. In the case of chronic conditions and fast-acting medicines for symptomatic treatment, it might be justified to collect evidence of efficacy from a trial treatment of a single patient. A “n of 1” is a clinical trial involving a single patient, i.e., a single case study. Through this service, patients with rare diseases would be able to receive treatment while at the same time testing the effectiveness of certain (expensive) medicines. During such an "n-of-1 trial" the physician alternately treats the patient with the off-label medicine and the medicine with which it is compared, for example, a placebo or treatment-as-usual. Rules are agreed in advance to allow for a fair comparison. The results of the trial treatment indicate whether the patient experiences benefits of the off-label medicine over and above treatment-as-usual. As series of trial treatments together bring more knowledge, these separate n-of-1 trials would be centrally coordinated and combined for analysis by an n-of-1 trial service. The current project is investigating whether such trial treatments, to be facilitated by the n-of-1 trial service, could be reimbursed by the Dutch basic health insurance. It is also examining whether the results of this type of research may be sufficient for authorities to decide on the effectiveness of an off-label medicine and its reimbursement for future patients with the rare disease in question. In a follow-up project, researchers hope to actually invite patients to participate in pilot trial treatments for neuromuscular diseases and eventually other diseases as well.

IRDiRC

The Netherlands Organisation for Health Research and Development (ZonMw) and the pharmaceutical enterprise Prosensa, are committed members of the IRDiRC.

Orphan medicinal products[26,27]

Orphan medicinal product committee

In 2011 the Steering Committee focused on the draft for a national plan in close cooperation with different stakeholders. However, it was decided that the Steering Committee would not be funded by the Dutch government after December 2011 and will no longer exist as a governmental committee from 2012 onwards. Stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise in the future with the Netherlands Organisation for Health Research and Development ZonMw taking more responsibility (with extra funding) and assuming a number of tasks from the former Steering Committee. Notably, the coordination of the development and implementation of a national strategy will be from 2012 onwards assumed by a secretariat at ZonMw.

Five grants have been awarded at the end of 2011 in the framework of the Orphan Designation Dossier (ODD) subsidy scheme.

[26] This section has been written using *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp53-62)

[27] This section was written using the Inventory of *Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp21-23)

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[28] The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.
[29] All websites and documents were last accessed in May 2012. A more detailed list of sources is available in the full report: http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf

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