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COMMISSION STAFF WORKING DOCUMENT

Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan mecidinal products — state of play 2015

Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products — state of play 2015

1. INTRODUCTION

This year marks the 15th anniversary of the Orphan Regulation,[1] which was adopted to encourage the development and authorisation of medicinal products for rare diseases. In that time, there has been impressive progress, in particular as regards generating significant activity by the pharmaceutical industry in this field.

It is estimated that 5 000 to 8 000 distinct rare diseases exist in the European Union. Although their prevalence is low, rare diseases affect 27 to 36 million people in the EU (6-8 % of the population).[2] The development of orphan medicinal products is therefore an important consideration for public health policy-makers seeking to address patients' needs.

In the course of the 1990s, a number of Member States adopted specific measures to improve our knowledge of rare diseases and their detection, diagnosis, prevention and treatment. Some of the relevant legislative or administrative provisions refer to 'orphan' or 'uneconomic drugs', but initiatives in this field were few and did not lead to significant progress in research on rare diseases.

Gradually, ministers started to recognise an urgent need for cooperation in this field across the European Union and between government and industry. On 23 February 1995, at the instigation of the European Commission department responsible for science, R&D and industry, an expert group was formed with the objective of discussing recommendations on priorities for EU-level research and regulatory action in the field of rare diseases and orphan drugs. The United States' effective Orphan Drug Act[3] was taken as an example of what could be done.

Commission proposals and strong political backing from the Council and the European Parliament led to the adoption of the Orphan Regulation on 16 December 1999. After 15 years of implementation and significant advances for patients, the Commission wishes now to take stock of progress in this field. Indeed, Article 9 of the Regulation requires it to publish regularly a detailed inventory of all EU and Member State incentives to support research into and the availability of orphan medicinal products (OMPs). The first inventory was published in January 2001 and updated versions were issued in 2003 and 2005. This paper thus represents the fourth version of the inventory; it includes information from the Commission's Directorates-General for Health and Food Safety and for Research and Innovation, and the European Medicines Agency (EMA), and also covers measures taken by Member State authorities.

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1 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

2 *2014 report on the state of the art of rare disease activities in Europe* (EUCERD joint action).

3 https://www.gpo.gov/fdsys/pkg/STATUTE-96/pdf/STATUTE-96-Pg2049.pdf

2. AIM OF THE ORPHAN REGULATION

The main objective of the Orphan Regulation is to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient in the EU.

It establishes a Union procedure for designating OMPs and proposes incentives for research in the field and the development and marketing of such products where the conditions that they address occur so infrequently that development and marketing costs are unlikely to be recovered through sales. In addition, the Regulation encourages Member States to adopt similar and/or complementary measures at national level.

OMPs can benefit from the incentives provided they are designated as such before the marketing authorisation is granted.[4] The key measures in the Regulation are:

- the establishing of an expert committee for OMPs within the EMA;
- EMA protocol assistance for sponsors of medicinal products on the conduct of the tests and trials necessary to demonstrate their quality, safety and efficacy, or regulatory assistance; advice can be free or given in return for reduced fees;
- 10 years of market exclusivity (in which other industry operators are prevented from entering the market with a similar product for the same therapeutic indication);
- access to a centralised procedure allowing immediate marketing authorisation in all Member States and facilitating the availability of medicines to all patients in the EU;
- a system of reduced fees for regulatory procedures (as payable under Community rules); and
- a repository of all designated and authorised OMPs.

3. UNION MEASURES

3.1. Incentives under the Orphan Regulation

The principal direct incentives introduced by the Orphan Regulation are as follows:

Designation procedure

Sponsors may apply to the EMA to have a product designated as an OMP. The designation process is free of charge.

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[4] Article 3 of the Regulation defines OMPs as follows:

A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Between 2000 and September 2015, the EMA received **2 302 applications for designation**, of which the Commission approved 1 544. Of these, **1 227** are currently active (some decisions have expired and some products have been withdrawn by the sponsor). Most designations were granted on the basis of the prevalence criteria (Article 3a). One was granted on the basis of the 'insufficient return on investment' criterion.

The sponsors of the designated products benefit from incentives such as protocol assistance to facilitate the development and authorisation of innovative medicines for the benefit of patients. The products can also more easily attract public or private funding; designation is a requirement for the EU's research framework programme, allows companies to secure R&D financing and creates opportunities for scientists to make important advances in treating the rare diseases in question.

The interest in this field is demonstrated by the steady increase in the number of requests over the years (see Tables 1 and 2).

The **Committee for Orphan Medicinal Products (COMP)** set up under the Regulation within the EMA has been in operation since April 2000 and is responsible for the scientific examination leading to designation. It was the first committee on which patients were represented (the Commission nominates three patient representatives for a three-year term).

The most frequently designated orphan conditions include acute myeloid leukaemia, cystic fibrosis, glioma, pancreatic carcinoma ovarian cancer, multiple myeloma, chronic lymphoblastic leukaemia and hepatocellular carcinoma. About a third of all applications concern some form of cancer (see Table 3).

Protocol assistance

On the basis of an orphan designation, a sponsor may ask for protocol assistance (scientific advice for orphan designated products) on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the product for marketing authorisation. Sponsors' uptake of protocol assistance has been extensive and is growing steadily. In the first 15 years of application of the Regulation, **951 protocol assistance** procedures were completed, of which **264** involved **SMEs**.

Fee waivers

Designation opens the way to possible **waivers** from fees associated with the marketing authorisation procedure, including those for protocol assistance, marketing authorisation, inspections, renewals, etc. The EMA receives a special annual contribution from the EU budget to waive fees in part or in full. Total reductions granted to date amount to **€78.4 million** (see Table 4).

Access to the centralised procedure (Union marketing authorisation)

Up to December 2005, 24 designated OMPs had received marketing authorisation (22 by centralised procedure and two by national procedures).

Under Regulation (EC) No 726/2004,[5] the centralised marketing authorisation procedure became mandatory for all such products throughout the EU as of 20 November 2005. Under this procedure, the Commission has to date **authorised 117 orphan medicines** for the benefit of patients suffering from rare diseases (see Tables 5 and 6), 82 % of which consist of new active substances. Some 25 orphan marketing authorisations are from SMEs.[6] The sponsors benefit from the incentives outlined above (e.g. fee waivers for regulatory procedures, 10-year market exclusivity).

The number of products authorised has grown over the years (which is encouraging for the future), but remains limited bearing in mind the existence of 5 000 to 8 000 distinct rare diseases (see Table 2). We can conclude that just 1 % of these are currently covered by authorised medicinal products in the EU. The incentives of the orphan drug legislation are therefore essential to facilitate pharmaceutical development.

The most frequently authorised medicinal products are treatments for pulmonary arterial hypertension, acute myeloid leukaemia, cystic fibrosis, multiple myeloma and acute or chronic lymphoblastic leukaemia.

Several OMPs[7] have been particularly important for public health and their innovative approach:

For cancer:

Glivec (imatinib) is indicated for the treatment of adult and paediatric patients with **chronic myeloid leukaemia**.

Revlimid (lenalidomide) is indicated for the treatment of adult patients with previously untreated **multiple myeloma**[8] who are not eligible for transplants.

For rare inborn errors of metabolism

Replagal (agalsidase alfa) or Fabrazyme (agalsidase beta) are indicated for the treatment of patients with a confirmed diagnosis of **Fabry Disease**.[9]

Vimizim (elosulfase alfa) is indicated for the treatment of **mucopolysaccharidosis**, type IVA[10] (Morquio A Syndrome, MPS IVA).

For blood disorders

Exjade (deferasirox) is indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with **beta thalassaemia**[11] **major** aged six years and older.

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5 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

6 The SME initiative started in 2005, so the EMA registered the first marketing authorisation from an SME in 2007.

7 Some of the examples mentioned no longer enjoy market exclusivity and are no longer OMPs.

8 Multiple myeloma is a malignant tumour of plasma cell characterised by overproduction of abnormal plasma cells in the bone marrow, and skeletal destruction.

9 Childhood, progressive, inherited, multisystemic lysosomal storage disease characterised by specific neurological, cutaneous, renal, cardiovascular, cochleo-vestibular and cerebrovascular manifestations.

10 Childhood inherited lysosomal storage disease characterised by progressive skeletal deformities, cervical instability, cardiovascular failure, respiratory problems, hepatomegaly, hearing loss and corneal clouding.

For the cardiovascular system

Revatio (sildenafil) for the treatment of **pulmonary arterial hypertension** and **chronic thromboembolic pulmonary hypertension**.

Market exclusivity

The most important incentive in the Regulation is 10-year **market exclusivity** for designated OMPs. Market exclusivity is unanimously regarded as crucial to any system of incentives for R&D on such products. The protection thus granted prevents the Union or a Member State from subsequently issuing or varying a marketing authorisation for a similar product (e.g. the same active substance) and for the same indication. At present, the OMPs authorised by the Commission benefit from market exclusivity.

Under Article 37 of the Regulation on medicinal products for paediatric use,[12] market exclusivity may be extended to 12 years if a paediatric investigation plan is completed.

Two medicinal products for which a paediatric investigation plan was completed, **TobiPodhaler** and **Xagrid**, currently enjoy extended (12-year) market exclusivity.

Workshops and international activities

The EMA has organised **11 workshops** to provide sponsors with guidance on issues such as the determination of prevalence, significant benefit and data collection, or more generally, e.g. the worldwide orphan medicinal designation workshop with the United States and Japan in 2014.

It is worth noting that many sponsors apply for orphan designation in the EU and elsewhere at the same time. The COMP has therefore developed international liaison on OMPs with medicines agencies in North America and Japan. It holds a monthly teleconference with the US Food and Drugs Administration.

3.2. European expert group on rare diseases

On 30 July 2013, the Commission adopted a decision on the setting-up of an expert group on rare diseases.[13] This repealed Decision 2009/872/EC on the former EU committee of experts on rare diseases (EUCERD), which in three years had adopted five recommendations and one opinion.

The role of the new expert group is to provide the Commission with advice and expertise in formulating and implementing the Union's activities in the field of rare diseases and to foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved. The group is composed of one representative per Member State, stakeholder (including patients') organisations and experts on rare diseases. To date, it has adopted three recommendations — on rare disease codification,[14] European reference networks[15]

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11 Childhood and infancy disease characterised by deficiency or absence of synthesis of the beta globin chains of hemoglobin. The condition is chronically debilitating and life-threatening, in particular due to the severe anaemia, the need for blood transfusions, and the complications related to these.

12 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

13 http://ec.europa.eu/health/rare_diseases/docs/dec_expert_group_2013_en.pdf.

14 http://ec.europa.eu/health/rare_diseases/docs/recommendation_coding_cegrd_en.pdf.

and cross border genetic testing of rare diseases[16] and rare disease registration and data collection[17].

3.3. EU-funded research on rare diseases and OMPs

Highlights

- Orphan designation has been a requirement for the Framework Programme funding since 2009.
- There was more than a 50 % increase in both the number of OMP applications submitted and the number of designations granted by Commission during 2009-2015, in comparison with 2000-2008.
- More than € 620 million in funding was awarded by FP7 to over 120 research projects on rare diseases and OMPs.
- Horizon 2020 maintains strong commitment to fund research on rare diseases and OMPs.

Seventh Framework Programme (FP7)

The EU supports research into rare diseases and OMPs through its multiannual framework programmes for research and technological development. Financial support is granted to project proposals that have been submitted in response to regular Commission calls and have successfully undergone peer-review evaluation by independent experts.

Under the Seventh Framework Programme for Innovation and Technological Development (FP7), which operated from 2007 to 2013, the Commission published several calls for proposals covering research into rare diseases and OMPs.

From the 2009 annual work programme onwards, orphan designation has been a requirement for funding in selected topics dealing with the preclinical and/or clinical development of substances with a clear potential as orphan drugs. This change has led to a significant increase in the number of designation requests received by the COMP.

Under FP7, **over €620 million** in support was granted to **over 120 collaborative research projects** on rare diseases and OMPs (see table 7). These included disease-driven and technology-driven projects, ranging from fundamental research into rare diseases to the preclinical and clinical development of orphan drugs. They basically covered all fields of medicine, e.g. oncology, neurology and neuromuscular medicine, endocrinology and metabolism, pulmonology,

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15 http://ec.europa.eu/health/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf.

16 http://ec.europa.eu/health/rare_diseases/docs/2015_recommendation_crossbordergenetictesting_en.pdf.

17 http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

gastroenterology, allergy and immunology, infectious diseases, haematology, molecular genetics, nephrology, urology, ophthalmology, dermatology. The EU funding facilitated the formation of multidisciplinary teams from universities, research organisations, SMEs, industry and patient organisations from across Europe and beyond.

Activities under the projects varied from collaborative research to coordination and networking, dissemination and the use of knowledge of rare diseases and OMPs. The EU-funded ERA-NET project E-RARE-2 aimed to develop and strengthen the coordination of national and regional research programmes. It launched joint transnational calls that involved funding agencies from 13 Member States, Turkey, Israel, Switzerland and Canada.

Horizon 2020

The EU will maintain a strong commitment to funding rare-disease research under Horizon 2020, its 2014-2020 framework programme for research and innovation. Horizon 2020 has already provided specific research opportunities in this area. Three projects are ongoing as a result of the rare disease related calls of the Work Programme 2014-2015: two collaborative projects SC0806, RETHRIM and the ERA-NET project E-RARE-3. Projects have been selected for funding from the PHC14-2015 call New Therapies for Rare Diseases in the fields: oncology, pulmonology, gastroenterology, immunology, haematology, ophthalmology, neurology and neuromuscular medicine. Further calls of the Work Programme 2016-2017 focusing on rare diseases are SC1-PM-03–2017 *Diagnostic characterisation of rare diseases* and SC1-PM-08–2017 *New therapies for rare diseases* are published[18].

International Rare Diseases Research Consortium (IRDiRC)

The Commission launched the International Rare Diseases Research Consortium (IRDiRC) under FP7, in cooperation with its EU and international partners. The IRDiRC brings together organisations that share common goals and principles and have agreed to work together in a multinational consortium. Its key objective is to deliver, by 2020, 200 new therapies for rare diseases and the means to diagnose most of them by stimulating, better coordinating and maximising the output of rare-disease research worldwide. The Commission chaired the IRDiRC from its establishment in early 2011 until 2013, when it handed over to Canada's Institute of Health.

Examples of research projects on OMPs:

The **AIPgene consortium** conducted a phase-1 clinical trial to test (a) the safety and (b) the efficacy of AAV5-AAT-PBGD in patients with severe acute intermittent porphyria (AIP), a rare genetic disorder in which mutations in the porphobilinogen deaminase gene produce insufficient activity of a protein necessary for heme synthesis. AIP is a life-threatening and chronically debilitating disease due to the severity of the symptoms and the long-term complications, including higher risk of cirrhosis and hepatocellular carcinoma.

In phase-1 and 2 clinical trials, the **ALPHA-MAN consortium** demonstrated the safety and clinical efficacy of the rhLAMAN, a biotechnologically derived recombinant human enzyme that is equivalent to a missing enzyme and introduced into the patients' bloodstream. The lysosomal storage disorder (LSD) alpha-Mannosidosis is a rare genetic disease caused by an enzyme defect

[18] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-health_en.pdf

due to mutations in the gene for lysosomal alpha-Mannosidase (LAMAN) affecting lysosomal and cellular glycoprotein catabolism, with severe consequences for the organism.

The **DevelopAKUre consortium** has been studying the efficacy and safety of the repurposed orphan designated drug Nitisinone, in order to obtain marketing authorisation for the treatment of patients with Alkaptonuria (AKU), a rare and debilitating Mendelian disease (also known as Black Bone Disease) involving early joint and bone damage and caused by deficiency in the homogentisate 1.2-dioxygenase (HGD) enzyme, leading to the accumulation of homogentisic acid (HGA).

3.4. Pricing and reimbursement

Under Article 168(7) of the Treaty, Member States are responsible for the formulation of health policy and the organisation and delivery of health services. This includes regulating the prices of medicines and their inclusion in health insurance systems. In line with the principle that Member States decide on the pricing, reimbursement and final placement of medicines on the market, the Commission has sought to promote and improve exchanges between them on best practices, knowledge and information concerning the pricing/reimbursement of orphan medicines.

In particular, it has supported voluntary cooperation between Member States and other relevant stakeholders (industry, patients, health professionals, insurers, etc.) in a project group on a mechanism for coordinated access to OMPs,[19] aimed at exchanging best practices on innovative OMP pricing and reimbursement policies. One outcome has been a 'transparent value framework' to facilitate decision-making at Member State level.

4. MEMBER STATES' MEASURES

The Commission has launched a survey to collect information on national measures to support research into, and the development and availability of, OMPs. Information has been collected through the Pharmaceutical Committee, the Commission's expert group on medicinal products. This information was based on Member States information validated by the relevant national competent authorities in December 2015. The Commission cannot vouch for its accuracy or completeness.

As regards measures to **support R&D,** some Member States have introduced reduced fees for registration and academic clinical trials, tax reductions or waivers, public funding for research and free scientific advice.

As regards measures to **support the availability** of OMPs to patients, many Member States have confirmed that they are implementing 'compassionate-use' programmes to bring unauthorised medicinal products to market. Such programmes are used for individual patients ('patient programmes') on the basis of a doctor's statement or the company can make products available to a group of patients. The cost of the product may or may not be reimbursed, depending on the Member State.

The impact of reimbursement on the availability of orphan medicinal products may be a matter of concern in the EU. The budgetary impact of OMPs is expected to rise due to the newly authorised

19 http://ec.europa.eu/DocsRoom/documents?locale=en&tags=Mechanism%20of%20coordinated%20access%20to%20orphan%20 medicinal%20products.

products in the coming years. In this context, it is important to highlight that some Member States have adopted specific measures for the reimbursement of OMPs.

Most Member States reported **other measures** that they have taken under national plans on rare diseases that cover not only OMPs, but also the prevention (e.g. pre-natal diagnosis) and detection of rare diseases, the exchange of information and cooperation with patients' organisations. In this context, most confirmed progress for the implementation of the Orphanet database and of centres of expertise for rare diseases and had registers of patients with particular diseases. This information is currently reflected in the 2014 report on the state of the art of rare disease activities in Europe[20] and is therefore not presented in this report.

Examples of national measures to support R&D and the availability of OMPs

In **Greece**, orphan drugs covered by a compassionate-use programme for individual patients are reimbursed in full.

In the **Netherlands**, the registration fee can be waived if the medicinal product is already registered in one or more other Member State and the prevalence of the condition is less than 1:150 000. High-tech start-ups qualify for tax reductions for R&D**.**

In **France**, OMP developers are exempt from certain taxes to be paid by pharmaceutical companies. In 2014, 10 of the 15 authorised OMPs were already available for patients thanks to the compassionate-use programme. France's pricing committee may agree to a high price for a medicinal product, but the company must agree to restrict its annual sales to a certain limit and supply all patients who are eligible for the treatment.

Belgium and the **Netherlands** have launched a pilot project on the joint procurement of OMPs.

In **Germany**, all OMPs are reimbursed directly after market authorisation.

Spain and **Sweden** have specific scientific advice procedures for potential OMPs, to provide scientific and regulatory support.

4.1. Austria

This Member State has not provided information.

4.2. Belgium

On 20 April 2015, in the margins of the European Council of Health Ministers in Riga, Belgium signed a bilateral agreement with the Netherlands on jointly assessing the potential added value of orphan drugs and negotiating with pharmaceutical companies the prices to be charged. This agreement, which was recently extended to Luxembourg, is a response to the current debate on cost-effectiveness and joint action.

Belgium also waives regulatory fees for OMPs and has an early-access procedure (authorisation phase and reimbursement) in cases of unmet medical need.

[20] http://ec.europa.eu/health/rare_diseases/docs/2014report_rare_disease_activitieseu_5_en.pdf.

4.3. Bulgaria

In Bulgaria, unauthorised medicinal products can be administered by a committee of three doctors from the relevant medical establishment for hospital care, at least one of whom has to have a recognised specialisation in the disease.

Public funding for orphan drugs comes from:

- the Health Ministry budget for the treatment of Bulgarian citizens for diseases outside the scope of mandatory health insurance; and
- the national health insurance fund.

A fund set up in 2004 provides organisational and financial support for the treatment of children up to the age of 18 who need diagnostic and therapeutic procedures that cannot be conducted in Bulgaria.

4.4. Croatia

Very expensive medicines, including OMPs, are financed from a dedicated fund.

4.5. Cyprus

Cyprus has introduced no independent measures to promote the development or stimulate the availability of OMPs. Nevertheless, public funding is available through the Cyprus Research Promotion Foundation (RPF) for basic research, pre-clinical trials, clinical trials, supply of materials, equipment and identifying collaboration and networking, etc. Moreover, Cyprus provides a named patient supply of medicinal products for pre-authorisation access.

4.6. Czech Republic

The pricing and reimbursement of OMPs is governed by the Act on Public Health Insurance. The average period from marketing authorisation to availability on the Czech market is two years. Accessibility is also supported by the waiving of regulatory fees, e.g. administrative fees are not charged for authorisations for the parallel import of an OMP. The administrative fee for applying to set the price and reimbursement level is waived and fees for scientific consultations can also be waived.

4.7. Denmark

Denmark provides pre-authorisation access to OMPs through compassionate use (‘patient supply’).

Patients with life-threatening diseases with no well-documented treatment option can be offered free experimental (named patient) treatment in highly specialised hospitals under certain circumstances.

All medicinal products with orphan designation are reserved for hospitals. Access to hospital and GP healthcare is free of charge for Danish citizens. The managed introduction of medicines to hospitals is quite simple and therefore quick.

The 2014 National Strategy for Denmark on Rare Diseases contains 97 recommendations, including on how to ensure access to necessary OMPs in Denmark. The strategy was developed in cooperation with patients’ organisations, healthcare professionals and other relevant parties. It

will be fully implemented by 2018 and the parties involved in its development will be consulted regularly in the years to come on progress made and obstacles encountered.

Denmark offers a full waiver of the annual fee for medicinal products with a small market share and a partial waiver for products with a limited market share.

4.8. Estonia

Applications for the reimbursement of OMPs can be submitted with appendices in English (not translated into Estonian, like applications for regular medicines). Also, the state can make an exception to the rule that the pharmaco-economical evaluation has to be tailored to conditions in Estonia.

4.9. Finland

This Member State has not provided information.

4.10. France

Under France's policy of incentives for the development of orphan drugs:

- OMP developers are exempt from the following taxes applying to pharmaceutical companies:
  i. tax on the turnover of medicinal products, if under €20 million;
  ii. tax on the promotion of medicinal products on the basis of promotion costs, if turnover under €30 million;
  iii. taxes paid on sales (no turnover threshold);
  iv. safeguard clause for medicinal products for which turnover is under €30 million;
  v. tax on direct sales for medicinal products for which turnover is under €30 million; and
  vi. tax on the distribution of medicinal products for which turnover is under €30 million.

  Scientific advice given at national level by the National Agency for the Safety of Medicine Products (ANSM) is free, regardless of whether the product is orphan;
- patients can be treated with medicinal products (orphan or not) before marketing authorisation is granted via compassionate-use programmes ('temporary authorisations for use' or ATUs). In 2014, 10 of the 15 authorised OMPs became available to patients early, thanks to ATUs; and
- the framework agreement between CEPS (the French pricing committee) and industrial representatives sets out some specific pricing procedures for OMPs: CEPS may agree to an OMP costing over €50 000 per patient per year where the price is similarly high abroad. In return, the company must agree:
  - to restrict its annual sales to a certain limit; and
  - to provide the drug to all patients who are eligible for treatment**.**

4.11. Germany

Germany has put in place a number of measures, such as fee reductions for activities involving medicinal products targeting rare diseases or under its national research programme. The ordinance on the compassionate use of medicinal products provides that no marketing

authorisation is required for products that are made available free of charge to patients with a seriously debilitating or life-threatening disease that cannot be treated satisfactorily with an authorised product.

Once authorised at European level, all OMPs are fully reimbursed by the statutory health insurance (GKV). Under the act on new regulations for the drug market (AMNOG), since 1 January 2011 all drugs with patented substances have been subject to cost/benefit analysis followed by price negotiation. However, while this procedure (limited to the 12 months following marketing authorisation) is ongoing, the product is still reimbursed at the price set by the manufacturer. OMPs with an annual turnover below €50 million are exempt from the cost/benefit analysis, as the benefit is taken for granted.

4.12. Greece

Greece's national measures for orphan drugs mainly consist of:

- a compassionate-use programme;
- special pricing conditions;
- special reimbursement conditions in the post-authorisation phase;
- no co-payment in the majority of cases; and
- the development of a national rare diseases plan.

The price list is fully revised twice a year, with the prices of medicines reduced to reflect those in the three EU countries with the lowest prices. Prices for new products, including orphan medicines, are set every four months approximately, depending on the number of applications received.

OMPs are priced on the basis of prices in at least two other Member States — unlike other medicinal products, for which prices from at least three other Member States are required.

4.13. Hungary

The National Institute of Pharmacy and Nutrition is considering the introduction of a reduction or a waiver of the fee paid by applicants for scientific advice.

Some programmes to simplify the access of patients with orphan diseases to unauthorised medicinal products, e.g. through named patient supply or an expanded access phase for medicines in clinical trials, are still under development. The compassionate-use programme will be regulated by national directives in the near future.

The competent authority maintains a service providing public and healthcare professionals with information on the availability of medicinal products for rare diseases in Hungary.

4.14. Ireland

Since 2010, €6.9 million has been invested in Ireland in research on a number of rare conditions and diseases (e.g. retinal degeneration, Battens Disease and Epidermolysis Bullosa). In November 2014, the Minister for Health announced €850 000 state investment for research on rare disease, with matching funding from five charities.

The Health Products Regulatory Authority advises and supports pharmaceutical companies as appropriate and operates a system of fee reductions or waivers for clinical trial applications.

Access to unauthorised medicines is provided in accordance with the specifications of a practitioner for individual patients or through participation in an approved clinical trial.

There are no specific policies for reimbursement. The National Centre for Pharmo-Economics (NCPE) facilitates healthcare decisions on the reimbursement of medicines. It assessed nine orphan medicines in 2014 (an increase from one in 2012 and five in 2013), almost all of which were approved for reimbursement.

4.15. Italy

The Health Ministry's most recent call for proposals for projects for rare diseases had funding of €8 million from the specific budget line dedicated to rare-disease research. Fees for national scientific advice procedures relating to OMPs are subject to a 50 % reduction.

Access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments, in particular the compassionate-use programme.

Italy has a dedicated fund for unauthorised orphan drugs awaiting approval; this is funded by marketing authorisation holders on the basis of overall expenditure for meetings and a conference (representing 5 % of that expenditure). In 2013, the fund amounted to around €17 million.

Orphan medicines are made available, though not reimbursed, within 60 days of the publication of the relevant Commission decision in the EU *Official Journal*. For OMPs, applications for pricing and reimbursement can also be submitted from the day of the EMA opinion (rather than the Commission decision, as is usually the case) and the procedure on pricing and reimbursement must take no more than 100 days.

In addition, the *Legge di Stabilità 2014* introduced an economic protection mechanism for the holders of marketing authorisations for OMPs on a list approved by the Italian Medicines Agency (AIFA) in February 2014. Where the national pharmaceutical expenditure ceiling is exceeded, those authorisation holders are excluded from the payback, which is instead distributed among holders of marketing authorisations in proportion to their respective pharmaceutical sales volumes.

4.16. Latvia

Latvia has put in place measures for the distribution of unauthorised medicines through a compassionate-use programme and some orphan medicines (notably for children) are reimbursed.

4.17. Lithuania

This Member State has not provided information.

4.18. Luxembourg

This Member State has not provided information.

4.19. Malta

Malta applies 70 % fee reductions for academic trials (which would include OMPs). Compassionate-use programmes and named patient supply are available.

Under a bilateral agreement with the UK, Malta has for some years been operating a 'treatment abroad' scheme for patients requiring tertiary-level healthcare, including treatment for rare conditions or complications.

In addition, the Maltese disease-based free medication scheme (Schedule V of the Social Security Act) has been revised to include families of diseases, so that sufferers of certain rare diseases can access treatment without waiting for the specific disease to be included in the Act.

4.20. The Netherlands

The Netherlands has for many years had a wide range of national measures in place as regards orphan diseases; these include:

- waiving the registration fee if the product is already registered in one or more other Member States and the prevalence of the indicated disease in the Netherlands is less than 1:150 000;
- possible tax reductions for R&D by high-tech start-ups;
- an innovative research incentives scheme based on a bottom-up approach and several subsidy schemes; and
- permission to market medicinal products that have not (yet) been granted marketing authorisation (compassionate-use programme):
    - on the basis of a doctor's statement; or
    - if the case involves a severe condition for which no alternative product is available on the market and the as-yet unauthorised product could be granted marketing authorisation in the future.

4.21. Poland

Poland has no national measures to support research into, or the development and availability of, OMPs or medicinal products that may be designated as such. Reimbursement decisions are taken by the Minister for Health according to the criteria in the Reimbursement Act. There is no separate budget for orphan drugs.

4.22. Portugal

A special-use authorisation procedure provides access to certain OMPs. If an OMP is not marketed in Portugal, the treating hospital can request special authorisation from the Portuguese Medicines Agency (Infarmed); if the use is approved, the OMP is supplied directly by the manufacturer and no co-payment is required of the patient.

Most orphan drugs in Portugal are dispensed at hospitals without any co-payment.

Since 2013, the National Institute of Public Health (INSA) in the Ministry of Health has had centres of expertise for lysosomal disorders (reference centres that might be part of future European reference networks) and a coordinating committee responsible for monitoring access to dedicated OMPs.

A specific card for the identification of people with rare diseases (*cartão para a pessoa com doença rara*) has streamlined access to clinical and OMP information for medical doctors and also in emergency situations.

4.23. Slovakia

Medicinal products to treat diseases with prevalence of less than 1:100 000 can be reimbursed from the public health insurance system. The costs can exceed the limit for other medicinal products. The product will be reimbursed for two years and then the reimbursement rate will be re-evaluated.

4.24. Slovenia

Slovenia's OMP measures include 50 % fee reductions for clinical trial applications, scientific advice, a compassionate-use programme and pricing provisions for low-volume medicines based on recognised medical needs.

4.25. Spain

Spain's national incentives for OMPs are:

1. measures to support R&D on OMPs:
   - Carlos III Institute of Health — Strategic Action in Healthcare for 2014 (financing for rare diseases):
     - health research projects (€4 322 422);
     - independent clinical research projects (€3 million);
     - platform of clinical trials formed by 30 research groups (€4 million); and
     - biomedical research network centre for rare diseases (€4 761 860);
   - a specific scientific advice procedure for potential OMPs operated by the Agency of Medicines and Medical Devices (AEMPS). The main objective of the advice is the early detection of developments that may require scientific/regulatory support from the AEMPS. Companies are also informed about regulatory tools and initiatives under the EU regulatory framework for OMP authorisation;
2. measures to support the availability of OMPs to patients:
   - AEMPS has developed a webportal to:
     - facilitate the application and management of these specific authorisations by providing common access;
     - reduce the administrative burden on stakeholders (companies, patients and healthcare professionals); and
     - increase transparency (the portal is a one-stop shop for information on the status of these specific authorisations in Spain).

4.26. Sweden

The Medical Products Agency provides incentives for academics, including fee waivers for clinical trial applications and free scientific advice for potential or designated OMPs. Patients can access treatment with OMPs by means of named-patient prescriptions or compassionate-use programmes.

4.27. Romania

An order of the Minister for Health on approval of the terms for the granting of authorisations for compassionate use and an order on addressing special needs (for a named patient or a group of

patients) provided for several means of access to OMPs. ‘Special needs’ medicines are products that have no marketing authorisation in Romania or are temporarily in short supply. Generally, the costs are not reimbursed.

As regards reimbursement, the list of international non-proprietary names (INNs) of prescription medicines provided to healthcare insurees and INNs provided in national healthcare programmes was updated in 2014 for the first time (after six years); 17 new molecules were introduced for the national programme for the diagnosis and treatment of rare diseases and serious sepsis.

A March 2015 amendment of the Minister for Health’s order on the approval of inclusion criteria facilitates the (conditional/unconditional) inclusion of orphan medicines in the list.

4.28. United Kingdom

The United Kingdom has no specific measures for orphan medicinal products, although they can benefit from free scientific advice or the new Early Access to Medicines Scheme (EAMS), which aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Under the scheme, the Medicines and Healthcare Products Regulatory Agency (MHRA) will give a scientific opinion on the benefit/risk balance of the medicine, on the basis of data available when the EAMS submission was made. The scientific opinion will be provided after a two-step evaluation process involving:

- ‘promising innovative medicine’ (PIM) designation; and
- an ‘early access to medicines’ scientific opinion.

ANNEX

TABLE 1: NUMBER OF APPLICATIONS SUBMITTED, APPLICATIONS WITHDRAWN, FINAL POSITIVE/NEGATIVE OPINIONS (2000-2015)

Year	*Applications submitted*	*Positive COMP opinions*	*Applications withdrawn*	*Final negative COMP opinions*	*Designations granted by Commission*
2000	72	26	3	0	14
2001	83	62	26	1	64
2002	80	43	32	2	49
2003	87	54	37	1	55
2004	108	75	22	4	73
2005	118	88	30	0	88
2006	104	81	20	2	80
2007	125	97	19	1	98
2008	119	86	31	1	73
2009	164	113	23	0	106
2010	174	123	51	2	128
2011	166	111	45	2	107
2012	197	139	52	1	148
2013	201	136	60	1	136
2014	329	196	62	2	187
2015[21]	175	136	62	1	138
Totals	**2 302**	**1 566**	**575**	**21**	**1 544**

[21] Data for the period from 1 January to 25 September 2015.

TABLE 2: NUMBER OF POSITIVE ORPHAN DESIGNATION DECISIONS BY THE COMMISSION, NEGATIVE OPINIONS AND WITHDRAWALS AFTER SUBMISSION (2000 TO 5.9.2015)

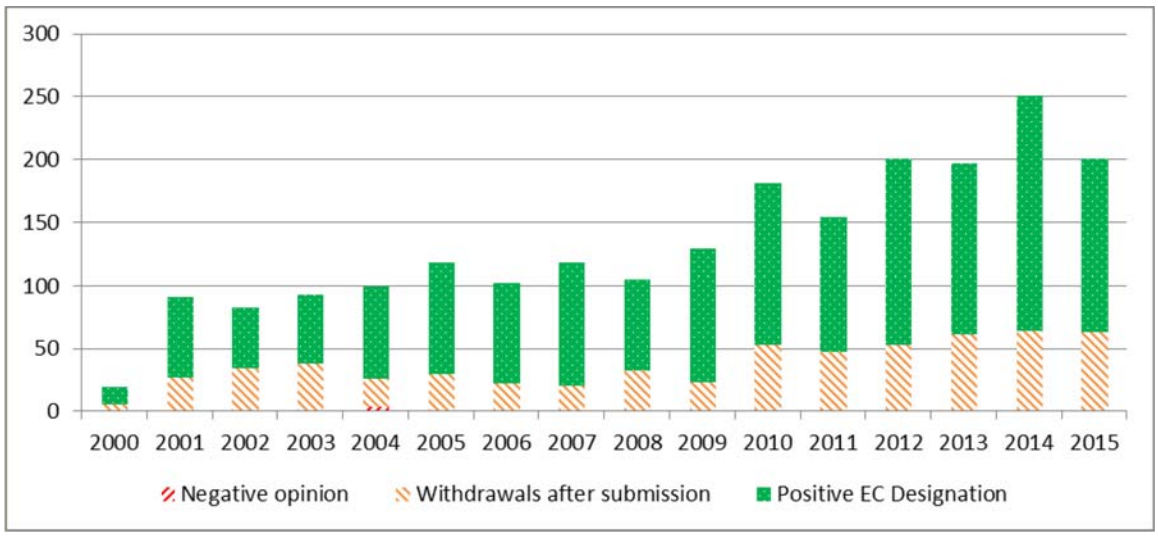

TABLE 3: DISTRIBUTION OF ORPHAN DESIGNATIONS PER THERAPEUTIC AREA

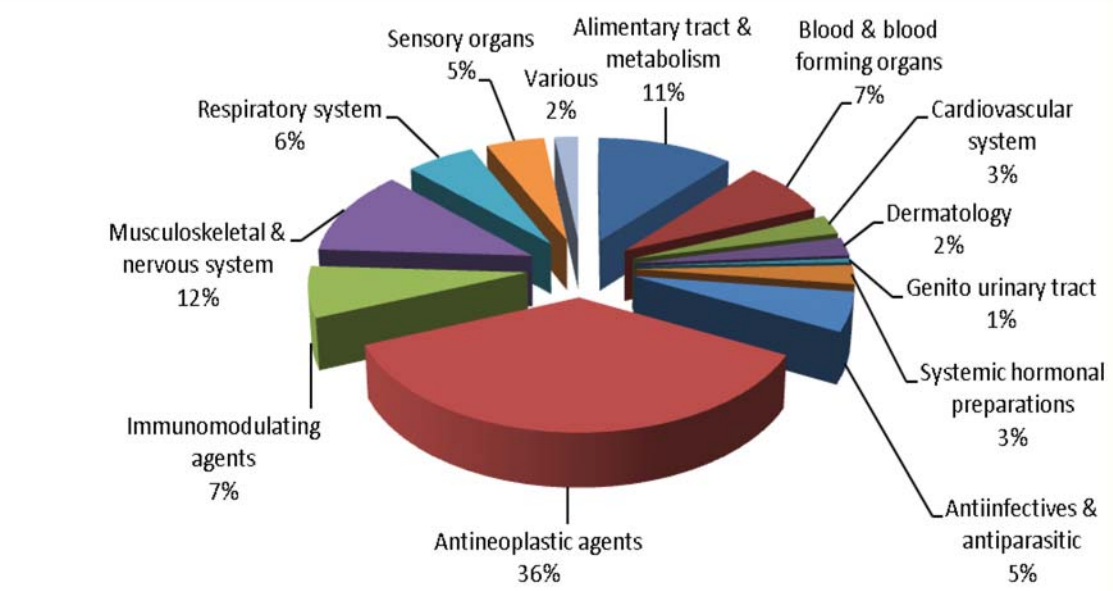

TABLE 4: FEE REDUCTIONS PROCESSED, 2000-2015 (INCLUDING PROTOCOL ASSISTANCE, ALL PRE- AND POST-AUTHORISATION ACTIVITIES)

Year	*EUR*	*Year*	*EUR*
2000	699 500	2008	4 767 500
2001	1 297 500	2009	6 347 200
2002	2 407 500	2010	6 742 800
2003	2 814 100	2011	4 719 605
2004	3 988 700	2012	7 490 720
2005	6 842 900	2013	6 677 360
2006	6 716 450	2014	9 432 260
2007	4 892 000	2015	13 228 960
		Total	**78 359 905**

TABLE 5: NUMBER OF MARKETING AUTHORISATIONS

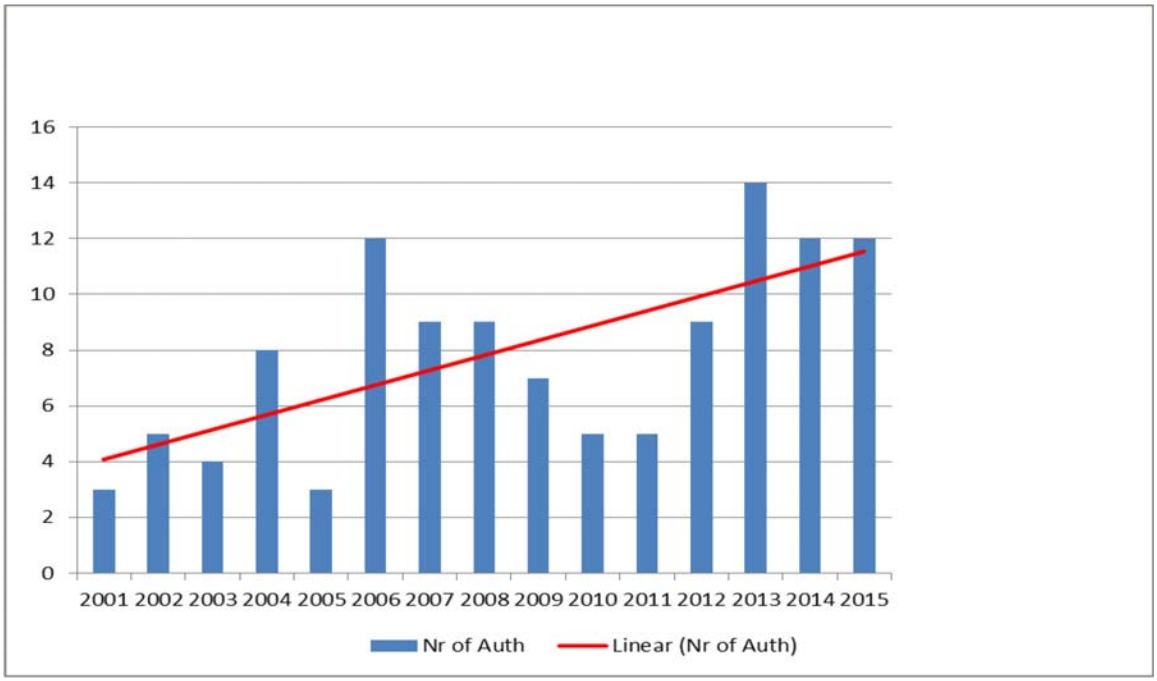

TABLE 6: LIST OF ORPHAN MARKETING AUTHORISATIONS

04-May-01	Fabrazyme	Active	Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.	Agalsidase beta
03-Aug-01	Replagal	Active	Replagal is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).	Agalsidase alfa
27-Aug-01	Glivec	Active	Glivec is indicated for the treatment of - adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. - adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. - adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy. - adult patients with relapsed or refractory Ph+ ALL as monotherapy. - adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. - adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRa rearrangement. The effect of Glivec on the outcome of bone marrow transplantation has not been determined. Glivec is indicated for - the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). - the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment. - the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.	Imatinib
05-Mar-02	Trisenox	Active	Induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptoralpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.	Arsenic trioxide
15-May-02	Tracleer	Active	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in: • Primary (idiopathic and heritable) pulmonary arterial hypertension • Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease • Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology	bosentan
20-Nov-02	Zavesca	Active	Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable. Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	Miglustat
13-Nov-02	Somavert	Active	Treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-I concentrations or was not tolerated.	Pegvisomant
24-Jan-03	Carbaglu	Active	Carbaglu is indicated in treatment of - hyperammonaemia due to N-acetylglutamate synthase primary deficiency. - hyperammonaemia due to isovaleric acidaemia. - hyperammonaemia due to methymalonic acidaemia. - hyperammonaemia due to propionic acidaemia.	Carglumic acid
10-Jun-03	Aldurazyme	Active	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I to treat the non-neurological manifestations of the disease	Laronidase
09-Jul-03	Busilvex	Active	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option. Busilvex following fludarabine (FB) is indicated as conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT) in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen. Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.	busulfan
16-Sep-03	Ventavis	Active	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.	Iloprost
17-Oct-03	Onsenal	Withdrawn	reduction of the number of adenomatous intestinal polyps in familial polyposis, as an adjunct to surgery and further endoscopic surveillance	Celecoxib

25-Mar-04	PhotoBarr	Withdrawn	Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO)	Porfimer sodium
28-Apr-04	Lysodren	Active	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.	Mitotane
14-Apr-04	Litak	Active	treatment of hairy cell leukaemia	Cladribine
29-Jul-04	Pedea	Active	Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age	Ibuprofen
13-Oct-04	Wilzin	Active	Treatment of Wilson's disease	Zinc acetate dihydrate
16-Nov-04	Xagrid	Active	Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk patient An at risk essential thrombocythaemia patient is defined by one or more of the following features: - > 60 years of age or - a platelet count > 1000 x 109/l or - a history of thrombo-haemorrhagic events.	anagrelide
21-Feb-05	Prialt	Active	Treatment of severe, chronic pain in adults who require intrathecal (IT) analgesia	ziconotide
21-Feb-05	Orfadin	Active	Treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT 1) in combination with dietary restriction of tyrosine and phenylalanine.	Nitisinone
13-Oct-05	Xyrem	Active	Treatment of cataplexy in adult patients with narcolepsy	Sodium oxybate
28-Oct-05	Revatio	Active	Adults Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. Paediatric population Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.	sildenafil
24-Jan-06	Naglazyme	Active	Naglazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome). A key issue is to treat children aged <5 years suffering from a severe form of the disease, even though children <5 years were not included in the pivotal phase 3 study. Limited data are available in patients < 1 year of age.	galsulfase
29-Mar-06	Myozyme	Active	Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). Myozyme is indicated in adults and paediatric patients of all ages.	alglucosidase alfa
29-May-06	Evoltra	Active	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis	clofarabine
19-Jul-06	Nexavar	Active	Hepatocellular carcinoma Nexavar is indicated for the treatment of hepatocellular carcinoma. Renal cell carcinoma Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Differentiated thyroid carcinoma Nexavar is indicated for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.	Sorafenib
19-Jul-06	Sutent	Active	Gastrointestinal stromal tumour (GIST) SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance. Metastatic renal cell carcinoma (MRCC) SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults. Pancreatic neuroendocrine tumours (pNET) SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.	sunitinib

			Experience with SUTENT as first-line treatment is limited.	
28-Jul-06	Savene	Active	Savene is indicated for the treatment of anthracycline extravasation	Dexrazoxane
10-Aug-06	Thelin	Withdrawn	Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.	Sitaxentan sodium
28-Aug-06	Exjade	Active	Treatment of chronic iron overload due to frequent blood transfusions (>=7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: - in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (>=7 ml/kg/month of packed red blood cells) aged 2 to 5 years, - in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older, - in patients with other anaemias aged 2 years and older. Treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.	deferasirox
20-Nov-06	Sprycel	Active	SPRYCEL is indicated for the treatment of adult patients with: - newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. - chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate. - Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.	Dasatinib
08-Jan-07	Elaprase	Active	Elaprase is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).	Idursulfase
04-Jan-07	Diacomit	Active	Diacomit is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.	Stiripentol
16-Jan-07	Inovelon	Active	adjunctive therapy in the treatment of seizures associated with Lennox Gastaut syndrome in patients 4 years and older.	Rufinamide
15-Feb-07	Cystadane	Active	Adjunctive treatment of homocystinuria, involving deficiencies or defects in: - cystathionine beta-synthase (CBS), - 5.10-methylene-tetrahydrofolate reductase (MTHFR), - cobalamin cofactor metabolism (cbl). Cystadane should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.	Betaine anhydrous
14-Jun-07	Revlimid	Active	Multiple myeloma Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Myelodysplastic syndromes Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.	Lenalidomide
20-Jun-07	Soliris	Active	Soliris is indicated in adults and children for the treatment of patients with - Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1). - Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).	Eculizumab
29-Jun-07	Siklos	Active	Siklos is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome	hydroxycarbamide
03-Aug-07	INCRELEX	Active	For the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD). Severe Primary IGFD is defined by: - height standard deviation score ≤ –3.0 and - basal IGF-1 levels below the 2.5th percentile for age and gender and - GH sufficiency. - Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test.	Mecasermin
22-Aug-07	Atriance	Active	Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has	nelarabine

			not responded to or has relapsed following treatment with at least two chemotherapy regimens. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.	
07-Sep-07	Gliolan	Active	Gliolan is indicated in adult patients for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).	5-aminolevulinic acid hydrochloride
17-Sep-07	Yondelis	Active	Yondelis is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. Yondelis in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.	Trabectedin
19-Nov-07	Tasigna	Active	Tasigna is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.	Nilotinib
19-Nov-07	Torisel	Active	Renal cell carcinoma: first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors Mantle cell lymphoma: treatment of adult patients with relapsed and/or refractory mantle cell lymphoma [MCL]	Temsirolimus
16-Apr-08	Thalidomide Celgene	Active	In combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged >= 65 years or ineligible for high dose chemotherapy. Prescribed and dispensed according to the Thalidomide Celgene Pregnancy Prevention Programme	Thalidomide
21-Apr-08	Volibris	Active	Volibris is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.	Ambrisentan
11-Jul-08	Firazyr	Active	Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).	icatibant
07-Oct-08	Ceplene	Active	Ceplene maintenance therapy is Indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.	Histamine dihydrochloride
02-Dec-08	Kuvan	Active	Kuvan is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment	sapropterin dihydrochloride
17-Dec-08	Vidaza	Active	Vidaza is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with: • intermediate 2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), • chronic myelomonocytic leukaemia (CMML) with 10 29 % marrow blasts without myeloproliferative disorder, • acute myeloid leukaemia (AML) with 20 30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification. Vidaza is indicated for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30 % marrow blasts according to the WHO classification.	Azacitidine
04-Feb-09	Nplate	Active	Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.	romiplostim
31-Mar-09	Ixiaro	Active	IXIARO is indicated for active immunisation against Japanese encephalitis for adults. Extension of indication of Ixiaro to the paediatric segment (2 months of age and older).	Japanese Encephalitis vaccine (inactivated, adsorbed)
06-Mar-09	Mepact	Active	MEPACT is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis	mifamurtide
02-Jul-09	Peyona	Active	Treatment of primary apnoea of premature newborns.	Caffeine citrate
31-Jul-09	Mozobil	Active	Mozobil is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly.	Plerixafor
03-Aug-09	Afinitor	Active	Hormone receptor-positive advanced breast cancer Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal	everolimus

			women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. Neuroendocrine tumours of pancreatic origin Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. Renal cell carcinoma Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.	
21-Sep-09	Cayston	Active	Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	aztreonam
23-Oct-09	Ilaris	Active	Cryopyrin-Associated Periodic Syndromes Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above, including: - Muckle-Wells Syndrome (MWS), - Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), - Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash. Systemic Juvenile Idiopathic Arthritis (SJIA) Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate. Gouty arthritis Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.	Canakinumab
23-Oct-09	Rilonacept Regeneron	Withdrawn	indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older	Rilonacept
23-Dec-09	Firdapse	Active	Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.	amifampridine
11-Mar-10	Revolade	Active	Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non splenectomised patients where surgery is contraindicated. Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1). Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).	Eltrombopag
15-Mar-10	Tepadina	Active	Tepadina is indicated, in combination with other chemotherapy medicinal products: - with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients; - when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.	Thiotepa
19-Apr-10	Arzerra	Active	Previously untreated chronic lymphocytic leukaemia (CLL): Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy. Refractory CLL: Arzerra is indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.	Ofatumumab
26-Aug-10	VPRIV	Active	VPRIV is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.	Velaglucerase alfa
20-Jul-11	TOBI Podhaler	Active	TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Tobramycin
28-Feb-11	Esbriet	Active	Esbriet is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).	Pirfenidone

02-Sep-11	Votubia	Active	Renal angiomyolipoma associated with tuberous sclerosis complex (TSC) Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume. Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) Votubia is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease related symptoms, has not been demonstrated.	Everolimus
03-Nov-11	Plenadren	Active	Treatment of adrenal insufficiency in adults.	hydrocortisone
16-Nov-11	Vyndaqel	Active	Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.	tafamidis
09-Mar-12	Xaluprine	Active	treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children	Mercaptopurine
24-Apr-12	Signifor	Active	Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.	pasireotide
13-Apr-12	Bronchitol	Active	Bronchitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.	Mannitol
23-Aug-12	Jakavi	Active	Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.	ruxolitinib
23-Jul-12	Kalydeco	Active	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.	ivacaftor
30-Aug-12	Revestive	Active	Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.	teduglutide
25-Oct-12	Glybera	Active	Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein.	Alipogene tiparvovec
24-Sep-12	Dacogen	Active	Dacogen is indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.	Decitabine
25-Oct-12	ADCETRIS	Active	Ttreatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).	Brentuximab vedotin
18-Dec-12	NexoBrid	Active	NexoBrid is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns.	Concentrate of proteolytic enzymes enriched in bromelain
02-Apr-13	Bosulif	Active	Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Bosutinib
01-Jul-13	Iclusig	Active	Iclusig is indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.	ponatinib
05-Aug-13	Imnovid	Active	Pomalidomide Celgene in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	Pomalidomide
06-Sep-13	Procysbi	Active	PROCYSBI is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.	mercaptamine (cysteamine bitartrate)
12-Sep-13	Orphacol	Active	Treatment of inborn errors in primary bile acid synthesis due to 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or $\Delta^4$3-Oxosteroid-5β-reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults	Cholic acid
28-Apr-14	Deltyba	Active	Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	delamanid

			Consideration should be given to official guidance on the appropriate use of antibacterial agents.	
18-Oct-13	Defitelio	Active	Treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy. It is indicated in adults and in adolescents, children and infants over 1 month of age.	defibrotide
21-Mar-14	Cometriq	Active	Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision	cabozantinib
27-Dec-13	Opsumit	Active	Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.	macitentan
04-Apr-14	Kolbam	Withdrawn	Kolbam is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.	cholic acid
07-Apr-14	Granupas	Active	Indicated for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Para-aminosalicylic acid
05-Mar-14	Sirturo	Active	SIRTURO is indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	bedaquiline
31-Jul-14	Translarna	Active	Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.	ataluren
27-Mar-14	Adempas	Active	Chronic thromboembolic pulmonary hypertension (CTEPH) Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with • inoperable CTEPH, • persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity. Pulmonary arterial hypertension (PAH) Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease	riociguat
28-Apr-14	Vimizim	Active	Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.	elosulfase alfa
22-May-14	Sylvant	Active	Sylvant is indicated for the treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus 8 (HHV 8) negative.	siltuximab
23-Jul-14	Gazyvaro	Active	Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy	obinutuzumab
21-Oct-14	IMBRUVICA	Active	IMBRUVICA is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo immunotherapy. IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo immunotherapy.	Ibrutinib
19-Dec-14	Cyramza	Active	Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.	ramucirumab
16-Dec-14	Lynparza	Active	Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based	Olaparib

			chemotherapy.	
19-Nov-14	Ketoconazole HRA	Active	Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.	ketoconazole
22-Dec-14	Scenesse	Active	Scenesse is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).	afamelanotide
26-Mar-15	Quinsair	Active	Quinsair is indicated for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adult patients with cystic fibrosis.	levofloxacin
19-Jan-15	Cerdelga	Active	Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).	eliglustat
15-Jan-15	Ofev	Active	Indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF)	Nintedanib
17-Feb-15	Holoclar	Active	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2 mm2 of undamaged limbus is required for biopsy.	Ex vivo expanded autologous human corneal epithelial cells containing stem cells
28-May-15	Lenvima	Active	LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).	lenvatinib
07-Jul-15	Hetlioz	Active	HETLIOZ is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in totally blind adults.	tasimelteon
28-Aug-15	Strensiq	Active	Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.	asfotase alfa
08-Sep-15	Raxone	Active	Raxone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON).	idebenone
14-Aug-15	Unituxin	Active	Unituxin is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). It is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.	dinutuximab
28-Aug-15	Farydak	Active	Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.	panobinostat
28-Aug-15	Kanuma	Active	Kanuma is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) Deficiency.	sebelipase alfa
	Obizur	Ongoing		
	Cresemba	Active	Treatment of - invasive aspergillosis - mucormycosis in patients for whom amphotericin B is inappropriate Consideration should be given to official guidance on the appropriate use of antifungal agents.	isavuconazole
	Blincyto	Ongoing		
	Kyprolis	Ongoing		
	Ravicti	Ongoing		

TABLE 7: FRAMEWORK PROGRAMME 7 – PROJECTS SUPPORTING RESEARCH INTO RARE DISEASES AND ORPHAN MEDICINAL PRODUCTS**

** **For m**ore information, see:
http://ec.europa.eu/research/health/pdf/rare-diseases-how-europe-meeting-challenges_en.pdf

Call identifier	Project acronym	Full Project Title	Project No
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**eurIPFnet**	European IPF Network: Natural course, Pathomechanisms and Novel Treatment Options in Idiopathic Pulmonary Fibrosis	**202224**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EUCILIA**	Pathophysiology of rare diseases due to ciliary dysfunction: nephronophthisis, Oral-facial-digital type 1 and Bardet-Biedl syndromes	**201804**
HEALTH-2007-2.4.5-9 Visual impairment and degeneration	**EuroVisionNet**	Visual Impairment and Degeneration: A Road-map for Vision Research within Europe	**200641**
HEALTH-2007-2.2.1-6 Neuron-glia interactions in health and disease	**CRUMBS IN SIGHT**	Restoring Mueller glia cell photoreceptor interactions with Crumbs	**200234**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**Euradrenal**	Pathophysiology and natural course of autoimmune adrenal failure in Europe	**201167**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EUROTRAPS**	Natural course, pathophysiology, models for early diagnosis, prevention and innovative treatment of TNF Receptor Associated Periodic Syndrome TRAPS with application for all hereditary recurrent fevers	**200923**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EUNEFRON**	European Network for the Study of Orphan Nephropathies	**201590**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EuroDSD**	Investigation of the molecular pathogenesis and pathophysiology of Disorders of Sex Development (DSD)	**201444**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EURO-PADnet**	The Pathophysiology and Natural Course of Patients with Primary Antibody Deficiencies (PAD)	**201549**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**Pemphigus**	Pemphigus — From autoimmunity to disease	**200515**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**EUCLYD**	A European Consortium for Lysosomal Disorders	**201678**
HEALTH-2007-4.1-4 Identifying patients' needs in the clinical trials context	**PatientPartner**	Identifying the Needs for Patients Partnering in Clinical Research	**201720**
HEALTH-2007-2.4.4-2 Research capacity-building in the field of rare diseases	**RareDiseasePlatform**	A European Platform of Integrated Information Services for Researchers in the Field of Rare Diseases and Orphan Drugs Supporting Team and Project Building.	**201230**
HEALTH-2007-2.4.4-1 Natural course and pathophysiology of rare diseases	**CureHLH**	European initiative to improve knowledge, treatment and survival of haemophagocytic syndromes in children	**201461**

HEALTH-2007-1.2-6 High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation	**NMD-Chip**	Development of targeted DNA-Chips for High Throughput Diagnosis of NeuroMuscular Disorders	**223026**
HEALTH-2007-4.2-1 Adapting of-patent medicines to the specific needs of paediatric populations	**LOULLA&PHILLA**	Development of 6-mercaptopurine and Methotrexate oral liquid formulations for the maintenance treatment of Acute Lymphoblastic Leukemia in children	**223401**
HEALTH-2007-1.4-5 Gene therapy tools targeting the central nervous system	**AAVEYE**	GENE THERAPY FOR INHERITED SEVERE PHOTORECEPTOR DISEASES	**223445**
HEALTH-2007-1.4-6 Stem cell lines for cell-based therapies	**NEuroStemCell**	European Consortium for Stem Cell Therapy for Neurodegenerative Diseases	**222943**
HEALTH-2007-1.2-6 High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation	**EURO-GENE-SCAN**	European Genetic Disease Diagnostics	**223293**
HEALTH-2007-1.4-4 Development of emerging gene therapy tools and technologies for clinical application	**PERSIST**	Persisting Transgenesis	**222878**
HEALTH-2007-1.4-6 Stem cell lines for cell-based therapies	**OptiStem**	Optimisation of stem cell therapy for clinical trials of degenerative skin and muscle diseases	**223098**
HEALTH-2007-2.2.1-7 Restorative approaches for therapy of neurodegenerative diseases	**Mitotarget**	Mitochondrial dysfunction in neurodegenerative diseases: towards new therapeutics	**223388**
HEALTH-2007-1.2-6 High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation	**TECHGENE**	High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation	**223143**
HEALTH-2007-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations	**NEUROSIS**	Efficacy and safety of inhaled budesonide in very preterm infants at risk for bronchopulmonary dysplasia	**223060**
HEALTH-2007-3.4-1 Disease networks of centres of reference HEALTH-2007-3.4-3 Patient mobility and access to information	**ENCE-CF-LAM-LTX**	European Networks of Centres of Expertise for CF (Cystic Fibrosis), LAM (Lymphangioleiomyomatosis), and LTX (Lung Transplantation)	**223355**
HEALTH-2007-2.1.2-5 Multidisciplinary fundamental genomics and molecular biology approaches to study basic biological processes relevant to health and diseases	**NeuroXsys**	Genomic Regulatory Systems of Human X-linked neurological diseases	**223262**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**BIO-NMD**	Identifying and validating pre-clinical biomarkers for diagnostics and therapeutics of Neuromuscular Disorders	**241665**

HEALTH-2009-2.4.4-1 Rare neurological diseases	**FIGHT-MG**	Myasthenias, a group of immune mediated neurological diseases: from etiology to therapy.	**242210**
HEALTH-2009-2.4.2-3 Translation of basic knowledge on inherited cardiomyopathies into clinical practice	**INHERITANCE**	INtegrated HEart Research In TrANslational genetics of dilated Cardiomyopathies in Europe	**241924**
HEALTH-2009-1.4-3 Activation of endogenous cells as an approach to regenerative medicine	**ENDOSTEM**	Activation of vasculature associated stem cells and muscle stem cells for the repair and maintenance of muscle tissue	**241440**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**TREATRUSH**	Fighting blindness of Usher syndrome: diagnosis, pathogenesis and retinal treatment (TreatRetUsher)	**242013**
HEALTH-2009-2.4.4-2 Preclinical development of substances with a clear potential as orphan drugs	**RDCVF**	Rod-derived Cone Viability Factor	**241683**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**LeukoTreat**	Therapeutic challenge in Leukodystrophies: Translational and ethical research towards clinical trials	**241622**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**MEFOPA**	European Project on Mendelian Forms of Parkinson's Disease	**241791**
HEALTH-2009-2.4.4-2 Preclinical development of substances with a clear potential as orphan drugs	**PRATH**	Preclinical study of Recombinant human Anti-C5 for the Treatment of atypical HUS	**242273**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**EFACTS**	European Friedreich's Ataxia Consortium for Translational Studies	**242193**
HEALTH-2009-3.2-4 Impact of cross-border collaboration on health services	**EUCBCC**	EUropean Cross Border Care Collaborations	**242058**
HEALTH-2009-2.4.4-1 Rare neurological diseases	**NIMBL**	Nuclease Immune Mediated Brain and Lupus-like conditions (NIMBL): natural history, pathophysiology, diagnostic and therapeutic modalities with application to other disorders of autoimmunity	**241779**
HEALTH-2009-2.1.2-1 Systems biology approaches for basic biological processes relevant to health and disease	**SYSCILIA**	A systems biology approach to dissect cilia function and its disruption in human genetic disease	**241955**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs. FP7-HEALTH-2010-single-stage	**PADDINGTON**	Pharmacodynamic Approaches to Demonstration of Disease-Modification in Huntington's Disease by SEN0014196	**261358**
HEALTH.2010.4.2-6 Impact of EU legislation on health research FP7-HEALTH-2010-single-stage	**Academic GMP**	The impact of Regulation (EC) No 1394/2007 on the development of Advanced Therapy Medicinal Products (ATMPs): an academic perspective	**260773**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs FP7-HEALTH-2010-single-stage	**ALPHA-MAN**	Clinical development of Enzyme Replacement Therapy in alpha-Mannosidosis patients using recombinant human enzyme.	**261331**
HEALTH.2010.2.4.4-2 ERA-Net on rare diseases FP7-ERANET-2010-RTD	**E-Rare-2**	ERA-Net on Rare Diseases	**266608**

HEALTH.2010.1.4-1 Translational research on cell-based immunotherapy FP7-HEALTH-2010-single-stage	**CELL-PID**	Advanced Cell-based Therapies for the treatment of Primary ImmunoDeficiency	**261387**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs FP7-HEALTH-2010-single-stage	**MABSOT**	Development of OPN-305 as an orphan drug for the treatment of Delayed Graft Function post solid organ transplantation	**261468**
HEALTH.2010.2.4.1-3 Structuring clinical research in paediatric and adolescent oncology in Europe FP7-HEALTH-2010-single-stage	**ENCCA**	EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS	**261474**
HEALTH.2010.2.4.1-5 Structuring clinical research on rare cancers in adults FP7-HEALTH-2010-two-stage	**ENS@T-CANCER**	European Network for the Study of Adrenal Tumours — Structuring clinical research on adrenal cancers in adults	**259735**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs FP7-HEALTH-2010-single-stage	**IMPACTT**	Immunoglobulin IgY pseudomonas A clinical trial for cystic fibrosis treatment	**261095**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs FP7-HEALTH-2010-single-stage	**AIPgene**	Augmenting PBGD expression in the liver as a Novel Gene therapy for Acute Intermittent Porphyria	**261506**
HEALTH.2010.1.2-3 Harmonisation, validation and standardisation in genetic testing FP7-HEALTH-2010-single-stage	**EuroGentest2**	Genetic testing in Europe — Network for the further development, harmonisation, validation and standardisation of services	**261469**
HEALTH.2010.4.2-2 International Paediatric initiative FP7-HEALTH-2010-single-stage	**GRIP**	Global Research in Paediatrics	**261060**
HEALTH.2010.2.1.2-1 Tackling Human Diseases through Systems Biology Approaches FP7-HEALTH-2010-two-stage	**Euro-MOTOR**	European multidisciplinary ALS network identification to cure motor neuron degeneration	**259867**
HEALTH.2010.2.4.4-1 Clinical development of substances with a clear potential as orphan drugs FP7-HEALTH-2010-single-stage	**GENEGRAFT**	Phase I/II ex vivo gene therapy clinical trial for recessive dystrophic epidermolysis bullosa using skin equivalent grafts genetically corrected with a COL7A1-encoding SIN retroviral vector (Orphan drug designation (EU/3/09/630))	**261392**
HEALTH.2010.4.2-3 Adverse Drug Reaction Research FP7-HEALTH-2010-single-stage	**EUROmediCAT**	EUROmediCAT: Safety of Medication use in Pregnancy in Relation to Risk of Congenital Malformations	**260598**
HEALTH.2011.2.4.1-1 Investigator-driven treatment trials for rare cancers	**IntReALL**	International study for treatment of childhood relapsed ALL 2010 with standard therapy, systematic integration of new agents, and establishment of standardised diagnostic and research	**278514**
HEALTH-2011.2.2.1-4 Creating clinical and molecular tools for experimental therapy of paediatric neurodegenerative disorders causing childhood dementia in Europe and India	**DEM-CHILD**	A Treatment-Oriented Research Project of NCL Disorders as a Major Cause of Dementia in Childhood	**281234**

HEALTH.2011.2.1.1-4 Population genetics studies on cardio-metabolic disorders in EU/AC and EECA populations	**InterPregGen**	Genetic studies of pre-eclampsia in Central Asian and European populations	**282540**
HEALTH-2011.2.2.1-1 Investigator-driven clinical trials for childhood-onset neurodegenerative diseases	**TIRCON**	Treat Iron-Related Childhood-Onset Neurodegeneration	**277984**
HEALTH.2011.2.4.1-1 Investigator-driven treatment trials for rare cancers	**EUROSARC**	European Clinical trials in Rare Sarcomas within an integrated translational trial network	**278742**
HEALTH.2011.1.4-2 Tools, technologies and devices for application in regenerative medicine	**InnovaLiv**	Innovative strategies to generate human hepatocytes for treatment of metabolic liver diseases: Tools for personalised cell therapy	**278152**
HEALTH-2011.4.2-1 Investigator-driven clinical trials on off-patent medicines for children	**TAIN**	Treatment of Adrenal Insufficiency in neonates-Development of a Hydrocortisone Preparation for the treatment of Adrenal Insufficiency in neonatesand infants.	**281654**
HEALTH.2011.2.4.1-1 Investigator-driven treatment trials for rare cancers	**IMMOMEC**	IMmune MOdulating strategies for treatment of MErkel cell Carcinoma	**277775**
HEALTH.2011.2.4.1-2 Translational research on cancers with poor prognosis	**OCTIPS**	Ovarian Cancer Therapy — Innovative Models Prolong Survival	**279113**
HEALTH.2011.2.4.1-2 Translational research on cancers with poor prognosis	**OPTATIO**	OPtimising TArgets and Therapeutics In high risk and refractOry Multiple Myeloma	**278570**
HEALTH.2011.2.4.1-2 Translational research on cancers with poor prognosis	**OVER-MyR**	Overcoming clinical relapse in multiple myeloma by understanding and targeting the molecular causes of drug resistance	**278706**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**chILD-EU**	Orphans Unite: chILD better together – European Management Platform for Childhood Interstitial Lung Diseases	**305653**
HEALTH.2011.1.4-1 Regenerative medicine clinical trials	**ESPOIR**	European clinical study for the application of regenerative heart valves	**278453**
HEALTH-2011.2.2.1-2 Understanding the role of neuroinflammation in neurodegenerative diseases	**NEURINOX**	NOX enzymes as mediators of inflammation-triggered neurodegeneration: modulating NOX enzymes as novel therapies	**278611**
HEALTH.2011.1.4-2 Tools, technologies and devices for application in regenerative medicine	**TissueGEN**	THE PRODUCTION OF A 3D HUMAN TISSUE DISEASE PLATFORM TO ENABLE REGENERATIVE MEDICINE THERAPY DEVELOPMENT	**278955**
HEALTH.2011.1.4-3 Development and production of new, high-affinity protein scaffolds for therapeutic use	**DARTRIX**	DARPin Targeted Magnetic Hyperthermic Therapy for Glioblastoma	**278580**
HEALTH.2012.1.4-2 Medical technology for transplantation and bioartificial organs	**BALANCE**	Development of a bioartificial liver therapy in acute liver failure	**304914**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a	**FIGHT-HLH**	First Targeted Therapy to FIGHT Hemophagocytic Lymphohistiocytosis (HLH): A novel approach to HLH	**306124**

clear potential as orphan drugs			
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**PROFNAIT**	Development of a prophylactic treatment for the prevention of fetal/neonatal alloimmune thrombocytopenia (FNAIT)	**305986**
HEALTH.2012.2.4.5-1 Technological approaches to combating sensory impairments Medical technology for transplantation and bioartificial organs	**DRUGSFORD**	Preclinical development of drugs and drug delivery technology for the treatment of inherited photoreceptor degeneration	**304963**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**DSD-Life**	Clinical European study on the outcome of surgical and hormonal therapy and psychological intervention in disorders of sex development (DSD)	**305373**
HEALTH.2012.2.1.1-1-B Clinical utility of -omics for better diagnosis of rare diseases	**EURenOmics**	European Consortium for High-Throughput Research in Rare Kidney Diseases	**305608**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**PREVENTROP**	New approach to treatment of the blinding disease Retinopathy of Prematurity (ROP)	**305485**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**STRONG**	European Consortium for the Study of a Topical Treatment of Neovascular Glaucoma	**305321**
HEALTH.2012.2.1.1-1-B Clinical utility of -omics for better diagnosis of rare diseases	**Neuromics**	Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases	**305121**
HEALTH.2012.2.1.1-1-A Support for international rare disease research	**SUPPORT-IRDiRC**	Support for international rare disease research to serve the IRDiRC objectives	**305207**
HEALTH.2012.1.2-1 Development of technologies with a view to patient group stratification for personalised medicine applications	**GAPVAC**	Glioma actively personalised vaccine consortium	**305061**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**EUROFANCOLEN**	Phase I/II Gene Therapy Trial of Fanconi anemia patients with a new Orphan Drug consisting of a lentiviral vector carrying the FANCA gene: A Coordinated International Action	**305421**
HEALTH.2012.1.2-1 Development of technologies with a view to patient group stratification for personalised medicine applications	**IMPROvED**	IMPROvED: IMproved Pregnancy Outcomes by Early Detection; personalised medicine for pregnant women: novel metabolomic and proteomic biomarkers to detect pre-eclampsia and improve outcome.	**305169**
HEALTH.2012.1.2-1 Development of technologies with a view to patient group stratification for personalised medicine applications	**THALAMOSS**	THALAssaemia MOdular Stratification System for personalised therapy of beta-thalassemia	**306201**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**DevelopAKUre**	Clinical Development of Nitisinone for Alkaptonuria	**304985**

HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**OPTIMISTIC**	Observational Prolonged Trial In Myotonic dystrophy type 1 to Improve QoL-Standards, a Target Identification Collaboration	**305697**
HEALTH.2012.1.4-4 Targeted nucleic acid delivery as an innovative therapeutic or prophylactic approach	**SKIP-NMD**	A phase I/IIa clinical trial in Duchenne muscular dystrophy using systemically delivered morpholino antisense oligomer to skip exon 53	**305370**
HEALTH.2012.2.1.1-1-C Databases, biobanks and 'clinical bio-informatics' hub for rare diseases	**RD-Connect**	RD-CONNECT: An integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research	**305444**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**BESTCILIA**	Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia	**305404**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**DeSScipher**	To decipher the optimal management of systemic sclerosis	**305495**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**Traumakine**	Interferon-beta treatment of acute respiratory distress syndrome (ARDS)	**305853**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**Net4CGD**	Gene Therapy for X-linked Chronic Granulomatous Disease (CGD)	**305011**
HEALTH.2012.2.4.4-2 Observational trials in rare diseases	**MeuSIX**	Clinical trial of gene therapy for MPS VI — a severe lysosomal storage disorder	**304999**
HEALTH.2012.3.2-2 New methodologies for health technology assessment	**ADVANCE_HTA**	Advancing and strengthening the methodological tools and practices relating to the application and implementation of Health Technology Assessment (HTA)	**305983**
HEALTH.2012.2.4.4-3 Best practice and knowledge sharing in the clinical management of rare diseases	**RARE-Bestpractices**	Platform for sharing best practices for management of rare diseases	**305690**
HEALTH.2012.2.4.4-1 Preclinical and/or clinical development of substances with a clear potential as orphan drugs	**ODAK**	Orphan Drug for Acanthamoeba Keratitis	**305661**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**BIOIMAGE-NMD**	BIOIMAGE-Neuromuscular Diseases	**602485**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**TheraGlio**	Microbubble driven multimodal imaging and theranostics for gliomas	**602923**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**MATHIAS**	New Molecular-Functional Imaging Technologies and Therapeutic Strategies for Theranostic of Invasive Apergillosis	**602820**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**MITIGATE**	Closed-loop Molecular Environment for Minimally Invasive Treatment of Patients with metastatic Gastrointestinal Stromal Tumours	**602306**

HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**CoMMiTMenT**	Combined Molecular Microscopy for Therapy and Personalised Medication in Rare Anaemias Treatments	**602121**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**MultISyn**	Multimodal Imaging of rare Synucleinopathies	**602646**
HEALTH.2013.4.2-3 New methodologies for clinical trials for small population groups	**ASTERIX**	Advances in Small Trials dEsign for Regulatory Innovation and eXcellence	**603160**
HEALTH.2013.4.2-3 New methodologies for clinical trials for small population groups	**IDEAL**	Integrated DEsign and AnaLysis of small population group trials	**602552**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**iPaCT**	Image-guided pancreatic cancer therapy	**603028**
HEALTH.2013.4.2-3 New methodologies for clinical trials for small population groups	**InSPiRe**	Innovative methodology for small populations research	**602144**
HEALTH.2013.0-1 Innovative paediatric clinical trials, new therapies, rare diseases, biomarker, personalised medicine, neuromuscular diseases	**SCOPE-DMD**	Consortium for Products across Europe in Duchenne Muscular Dystrophy	**601573**
HEALTH.2013.0-1 Boosting the translation of health research projects' results into innovative applications for health	**ASPRE**	Combined Multi-marker Screening and Randomised Patient Treatment with Aspirin for Evidence-based Pre-eclampsia Prevention	**601852**
HEALTH.2013.1.2-1 Development of imaging technologies for therapeutic interventions in rare diseases	**BETACURE**	Personalised diagnosis and treatment of hyperinsulinemic hypoglycaemia caused by beta-cell pathology	**602812**
HEALTH.2013.1.3-3 Safety and efficacy of therapeutic vaccines	**MYASTERIX**	Clinical safety, immunogenicity and efficacy of a therapeutic vaccine that combines peptides mimicking antigen receptors on autoimmune B and T cells associated with myasthenia gravis	**602420**
HEALTH.2013.1.3-3 Safety and efficacy of therapeutic vaccines	**SYMPATH**	Reach α-synuclein-dependent neurodegeneration: clinical development of therapeutic AFFITOPE vaccines for Parkinson's disease and multisystem atrophy	**602999**
HEALTH.2013.1.4-1 Controlling differentiation and proliferation in human stem cells intended for therapeutic use	**REPAIR-HD**	Human pluripotent stem cell differentiation, safety and preparation for therapeutic transplantation in Huntington's disease	**602245**
HEALTH.2013.1.4-1 Controlling differentiation and proliferation in human stem cells intended for therapeutic use	**NEUROSTEMCELLREPAIR**	European stem cell consortium for neural cell replacement, reprogramming and functional brain repair	**602278**
HEALTH.2013.2.1.1-1 Functional validation in animal and cellular models of genetic determinants of diseases and ageing processes	**SYBIL**	Systems biology for the functional validation of genetic determinants of skeletal diseases	**602300**

HEALTH.2013.2.1.1-1 Functional validation in animal and cellular models of genetic determinants of diseases and ageing processes	**CAM-PAC**	Integrative Analysis of Gene Functions in Cellular and Animal Models of Pancreatic Cancer	**602783**
HEALTH.2013.2.2.1-4 Patho-physiology and therapy of epilepsy and epileptiform disorders	**EPISTOP**	Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy — tuberous sclerosis complex	**602391**
HEALTH.2013.2.3.1-2 Stratified approaches to antibacterial and/or antifungal treatment	**CFMATTERS**	Cystic Fibrosis Microbiome-determined Antibiotic Therapy Trial in Exacerbations: Results Stratified.	**603038**
HEALTH.2013.2.4.1-1 Investigator-driven treatment trials to combat or prevent metastases in patients with solid cancer	**EEC**	EURO EWING Consortium — International Clinical Trials to Improve Survival from Ewing Sarcoma	**602856**