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SCIENCE MEDICINES HEALTH

An European Perspective on Orphan Medicinal Products

National Regulatory Conference, Selangor, Malaysia (4th of August of 2015)

Presented by Bruno Sepodes
Chair of the Committee of Orphan Medicinal Products (COMP) / CHMP & CAT Member

An agency of the European Union

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The European Medicines Agency

- EMA is an interface of co-ordination of Member States activities with respect to medicines (assessment responsibility for some procedures)
- European Agency Decentralised Administration - not part of the European Commission (decision making body)
- Centralized procedure: 1 application to the EMA → Marketing Authorization in all EU Member States

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What is a rare disease?

EU definition:

- Medical condition affecting **not more than** 5 in 10,000 persons in the European Community (around 252,000 people)

US definition:

- The disease or condition for which the drug is intended affects fewer than 200,000 people in the US (around 6.4 in 10,000)

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What is different about rare diseases?

- Diseases are usually poorly or incompletely understood
  Generally, the lower the prevalence, the less well we tend to understand them
- Small populations
  Limited opportunity for study and replication
- Highly heterogeneous group of disorders
  ~7000 different diseases
  Often high phenotypic diversity within individual disorders
- Usually little precedent for drug development within individual disorders
- Development often requires more (and more careful) planning than non-Orphan

Need a solid scientific base upon which to build an overall program

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Why an orphan regulation?

"Society cannot accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. It is therefore up to the public authorities to provide the necessary incentives and to adapt their administrative procedures so as to make it as easy as possible to provide these patients with medicinal products which are just as safe and effective as any other medicinal products and meet the same quality standards."

EU Charter of Fundamental Rights

EMA

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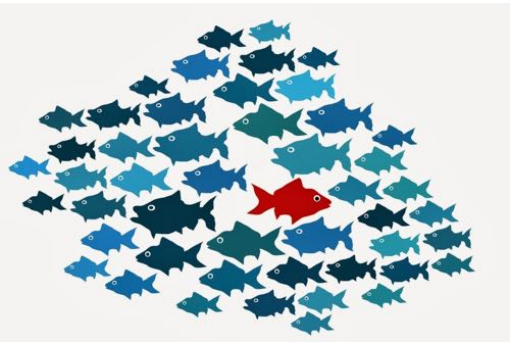
Why an orphan regulation?

- Rare diseases → developing and marketing cost would not be recovered by the expected sales

(products are called *orphans*, they do not have "developers")

- Persons suffering from rare conditions deserve same quality of treatment as other patients

- Pharmaceutical industry does not develop medicines for rare diseases under normal market conditions



EMA

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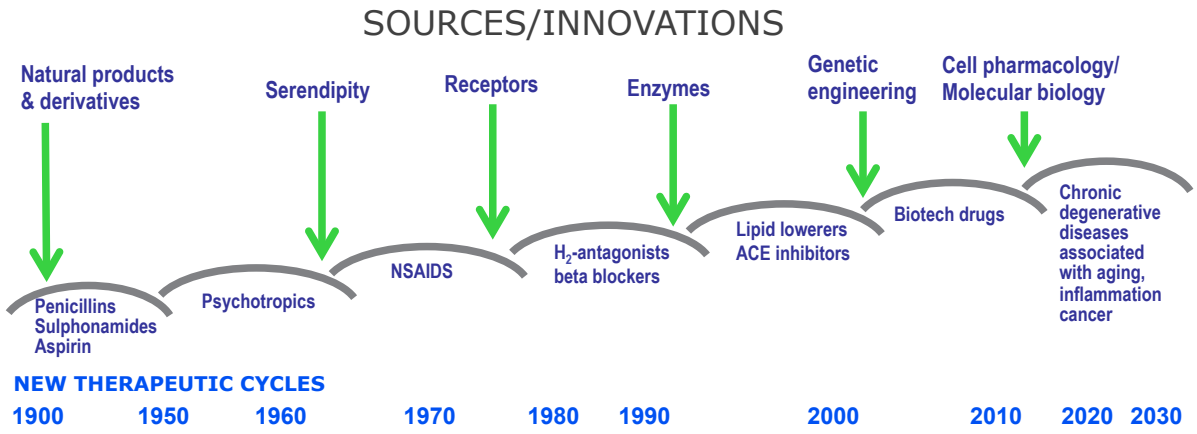
Drug innovation & therapeutic cycles



Source: Lehman Brother Pharmaceutical Research

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Early history

- Rare diseases have often led the way for medical advances
- Early example – LDL cholesterol and atherosclerosis
  - 1938, **Carl Müller** described familial hypercholesterolemia (FH)
  - circa 1963, **Avedis Khachadurian** described 2 FH forms: homozygous (HoFH) and heterozygous (HeFH)
  - 1985, **Joseph Goldstein** and **Michael Brown** shared a Nobel Prize in Medicine for research on genetic regulation of cholesterol metabolism

Identified HMG-CoA reductase and inability to remove LDL from the blood in HoFH children and their HeFH parents[1]

[1]Goldstein JL, Brown MS, Proc Natl Acad Sci USA 1973;70(10):2804-2808

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Early history

- 1987, lovastatin first HMG-CoA reductase inhibitor approved in USA
- ~ 60 million Americans receiving lipid-lowering therapy
- All-time highest grossing prescription drugs in US

1. Atorvastatin (Lipitor) $7.2 billion
2. Esomeprazole (Nexium) $6.3 billion
3. Clopidogrel Plavix $6.1 billion
4. Rosuvastatin (Crestor) $3.8 billion

10. Erythropoietin alfa (Epogen) $3.3 billion

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Early history

- HoFH – 1 in a million
- 2 new drugs approved in US for its treatment / 1 new in EU (other refused)
  - LDL apheresis, liver transplantation
  - Anti-sense oligonucleotide (AON) (mipomersen)[2] (targets mRNA for apolipoprotein B)
  - Microssomal triglyceride transfer protein (MTP) inhibitor (lomitapide)[3] (MTP necessary for VLDL assembly and secretion)
- HeFH ~ 1:500 in many populations
  - Numerous therapeutics, e.g., statins, bile acids, other drugs
- Investigational agents in clinical trials in HoFH
  - Clinicaltrials.gov lists studies in various phases, e.g., Phase 3

[2]Visser ME et al. Eur Heart J 2012;33(9):1142-1149
[3]Cuchel M et al. N ENgl J Med 2007;356(2):148-156

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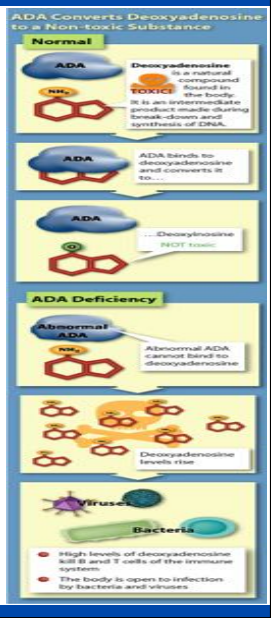
Early history

- Example: Adagen for adenosine deaminase deficiency (ADA)
- Population: 1:2x10^5 to 1:1x10^6 born with homozygous mutation.
- Causes Severe Combined Immunodeficiency (SCID)
- Adagen is one of the first orphan drugs (based on n=12!); enzyme replacement therapy.

US designation in 1984



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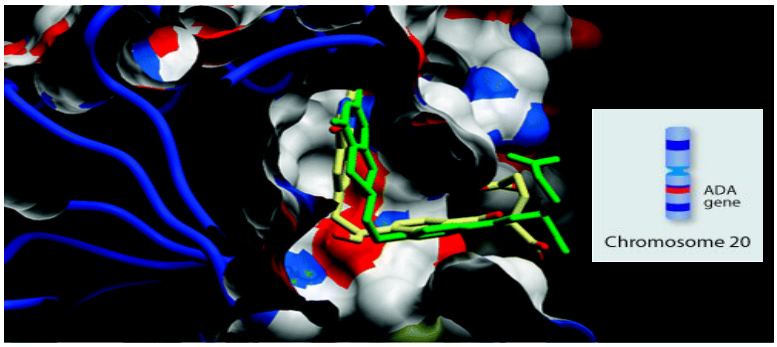
Adenosine deaminase deficiency



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ORIGINAL ARTICLE

Previous | Volume 360:447-458 January 29, 2009 Number 5 | Next

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alma Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the *ADA* gene into 10 children with SCID due to ADA deficiency who lacked an HLA-

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Mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)

Mucopolysaccharidosis, liposomal storage disorder.

Estimated only 1,100 persons world-wide.

Enzyme replacement can prevent these changes

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Naglazyme for MS Type VI (Maroteaux-Lamy syndrome)

COMP
Orphan

Active substance	N-acetylgalactosamine 4-sulfatase
Medicine Name	Naglazyme
Disease/condition	Treatment of mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy syndrome
Date of decision	14/02/2001
Outcome	Positive
Orphan decision number	EU/3/01/025

CHMP
B/R

Name	Naglazyme
Agency product number	EMEA/H/C/000640
Active substance	galsulfase
International non-proprietary name (INN) or common name	galsulfase
Therapeutic area	Mucopolysaccharidosis VI
Anatomical therapeutic chemical (ATC) code	A16AB
Additional monitoring ▼	This medicine is under additional monitoring. This means that it is being monitored even more intensively than other medicines. For more information, see medicines under additional monitoring.
Treatment of rare diseases D	This medicine has an "orphan designation" which means that it is used to treat life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union, or are medicines which, for economic reasons, would be unlikely to be developed without incentives.
Exceptional Circumstances E	There were "exceptional circumstances" concerning the approval of this medicine. This happens when the applicant can show that they are unable to provide comprehensive data on the efficacy and safety of the medicine for which authorisation is being sought, due to the rarity of the condition it is intended for, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data.

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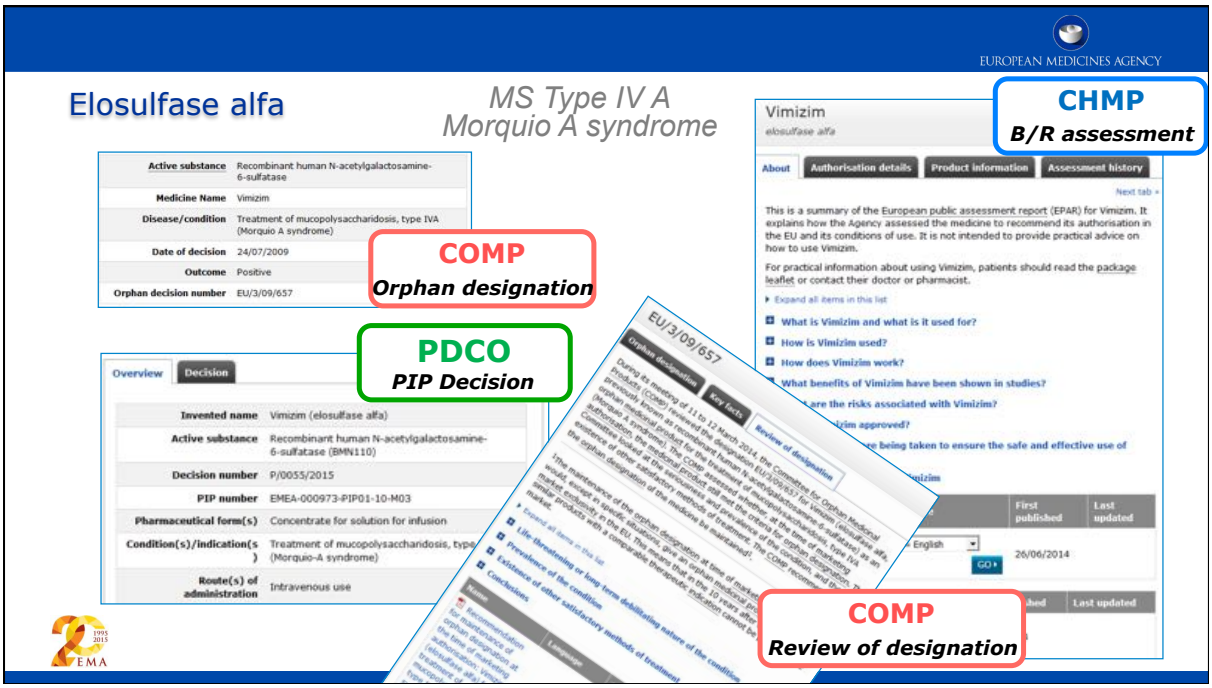
Enzyme Replacement Therapies

Some of the most extraordinarily expensive treatments in the history of mankind @ the time (some ≈ $400,000/patient/year).

FDA/EMA does not regulate price.

Radically transformative beneficial to patients lives.

Market Exclusivity lasts 7/10 years; ***knowledge gained is eternal!***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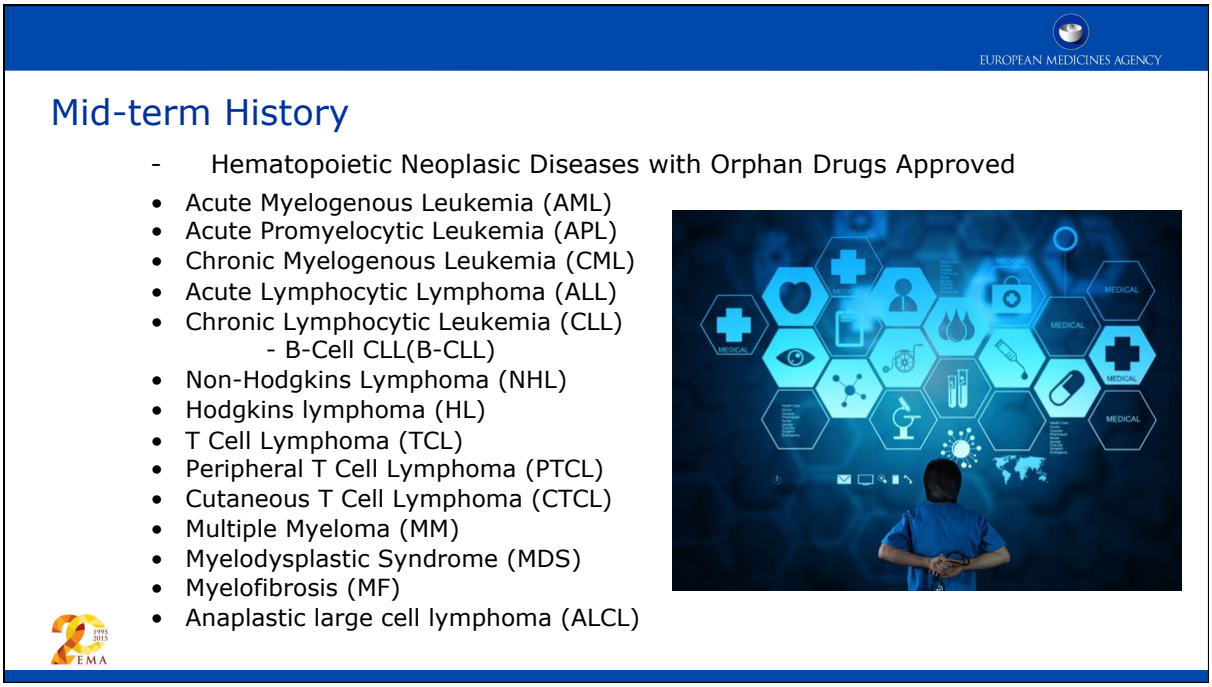
Elosulfase alfa
MS Type IV A
Morquio A syndrome
CHMP
B/R assessment
COMP
Orphan designation
PDCO
PIP Decision
COMP
Review of designation
Vimizim
elosulfase alfa
About
Authorisation details
Product information
Assessment history
Active substance
Recombinant human N-acetylgalactosamine-6-sulfatase
Medicine Name
Vimizim
Disease/condition
Treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome)
Date of decision
24/07/2009
Outcome
Positive
Orphan decision number
EU/3/09/657
Overview
Decision
Invented name
Vimizim (elosulfase alfa)
Active substance
Recombinant human N-acetylgalactosamine-6-sulfatase (BMN110)
Decision number
P/0055/2015
PIP number
EMEA-000973-PIP01-10-M03
Pharmaceutical form(s)
Concentrate for solution for infusion
Route(s) of administration
Intravenous use
EU/3/09/657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Mid-term History
- Hematopoietic Neoplasic Diseases with Orphan Drugs Approved
• Acute Myelogenous Leukemia (AML)
• Acute Promyelocytic Leukemia (APL)
• Chronic Myelogenous Leukemia (CML)
• Acute Lymphocytic Lymphoma (ALL)
• Chronic Lymphocytic Leukemia (CLL)
- B-Cell CLL(B-CLL)
• Non-Hodgkins Lymphoma (NHL)
• Hodgkins lymphoma (HL)
• T Cell Lymphoma (TCL)
• Peripheral T Cell Lymphoma (PTCL)
• Cutaneous T Cell Lymphoma (CTCL)
• Multiple Myeloma (MM)
• Myelodysplastic Syndrome (MDS)
• Myelofibrosis (MF)
• Anaplastic large cell lymphoma (ALCL)
MEDICAL

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Mid-term History

- Orphan drugs that have changed practice standards

(partial list)

- Imatinib for Chronic Myelogenous Leukemia (CML)
- All-Trans Retinoic Acid and ASO_3 for Acute Promyelocytic Leukemia (APL)
- Rituximab for Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkins Lymphoma (NHL)
- Azacitidine, decitabine and lenalidomide for Myelodysplastic Syndrome (MDS)
- Bortezomib, phenylalanine mustard, thalidomide and lenalidomide for Multiple Myeloma (MM)

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Principles on European orphan drug designation

Objective of **Regulation (EC) No 141/2000**

- provide incentives that stimulate research and development
- modify market conditions
- set up system of recognition for orphan medicines to be eligible for incentives:
  - Rarity (not more than 5 in 10,000)
  - Seriousness (life threatening / chronically debilitating)
  - Existence of alternative methods of treatment (significant benefit?)

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Legal references in the EU

Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999

Commission Regulation (EC) No 847/2000 of 27 April 2000

Commission communication July 2003 (2003/C 178/02)

Commission communication on Art 8(1) and (3) (C(2008) 4077)

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Main characteristics orphan designation

For medicinal products for human use

Procedure free of charge

Can be requested at any stage of development

Sponsor can be either company or individual

- *Established in the Community (EU, Iceland, Liechtenstein, Norway)*

European Commission Decision gives access to incentives

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EU main Incentives
Orphan designated Medicinal Products (OMP)

Fee reductions:

Application for OMP Designation (OD):100%

Protocol assistance (PA) from the EMA: 100% for SMEs,

75% for non-SMEs

Application for Marketing Authorisation (MAA):

100% for SMEs,10% for non-SMEs

EU marketing authorisation (mandatory)

10 (+2) year Market Exclusivity in the EU

Access to EU research programmes

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Table 1. **Features of orphan drug incentive systems[1] in the USA[a] and EU[b]**

Feature	USA	EU
Programme established	1983 — the Orphan Drug Act modified the Federal Food, Drug and Cosmetic Act	2000 — Orphan Medicinal Products Regulation
Prevalence criterion for rare disease	<200 000 patients in the USA (<7.5:10 000)	Life-threatening or chronically debilitating disorder that affects <5:10 000 in the EU
Requirements for orphan drug designation	Rare disease, or research and development costs cannot be recovered in 7 years	Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit
Products eligible for orphan drug designation	Drugs and biologicals (including vaccines and in-vivo diagnostics)	Drugs and biologicals (including vaccines and in-vivo diagnostics)
Market exclusivity	7 years; prevents same product being approved for the same indication unless clinical superiority is shown	10 years; can be reduced to 6 years if orphan drug criteria no longer met
Other benefits	Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharmaceutical companies and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food	Regulatory fees can be reduced or waived; access to centralized procedure; protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products.

[a] USA = United States of America.
[b] EU = European Union.

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	Singapore	South Korea	Taiwan
Legal framework	Medicines Act (Chapter 176, Section 9: (Orphan Drugs Exemption) (1991)	MFDS Notification No. 2013/222 Provision on Designation of Orphan Drugs (1998) Orphan Drug Provision of designation 2013	Rare Disease Control and Orphan Drug Act (2000)
Authorities involved	MoH	MFDS/KFDA	TFDA/DOH
Prevalence of the disease justifying the orphan status	less than 20,000	less than 20,000	1/10,000
Marketing exclusivity	No	No 6 years for data reexamination for NCE	10 years
Tax credit	No	No	No
Grants for research	No	Very few precedent of national funded research programs	Financial subsidies for local R&D for orphan drugs
Accelerated marketing procedure	Yes	Yes	Yes
Challenges /expected updates	Clarification on the OD definition for consistency across designation More incentives, such as marketing exclusivity or subsidies in the orphan drug policy	Long designation process up to 9 months	Local clinical data sometimes required No exemption of manufacturing sites registration which can significantly impact the registration timeline

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Lessons learned from 15 years of the Orphan Regulation

Stakeholders & Development of Orphan Drugs in the EU

2000

Patients: few drugs

Industry: major 'Big Pharma' & development of *blockbusters*

Health care professionals/ Academia: not involved

Regulators: at least 28 different procedures for MA

July 2015

Patients: 105 'active' OD, > 1500 products designated

Industry: major SMEs and Academia involvement – 2/3 of designations

Health care professionals/ Academia: Sponsors of designations / some are MAH

Regulators: 1 procedure – centralised

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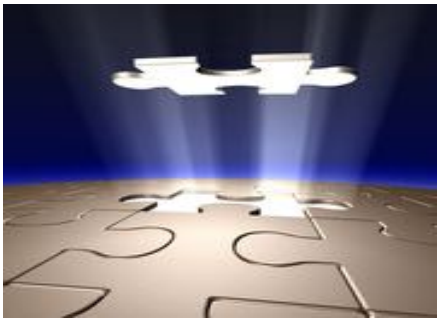
Oportunities for patients

- Benefits for more than 30 millions of patients' in the EU
- Potential benefits for neglected diseases
- Model for other geographic areas
- Model for other more prevalent diseases



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Stimulation of innovation

- Fusion proteins
- Monoclonal Antibodies
- Gene and cell therapy
- Oligonucleotides
- Tissue engineering
- etc.

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Committee of Orphan Medicinal Products (COMP)

- 1 elected Chair + EMA Scientific Secretariat
- 1 Representative per Member State
- 3 Patients' Representatives appointed by Eur. Commission
- 3 Members appointed by European Commission on proposal from Agency
- 1 Member for Norway and 1 for Iceland

Total: 33 members + 2 non voting

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Patients engagement with EMA committees and working parties

COMP: Committee of Orphan Medicinal Products

3 Patient Representatives as Members + 2 Observers

PDCO: Committee of Paediatric Medicinal Products

3 Patient Representatives as Members + 3 Alternates

CAT: Committee of Advanced Therapies

2 Patient Representative as Member + Alternate

PRAC: Pharmacovigilance Risk Assessment Committee

1 Patient Representative as Member + Alternate

PCWP: Patients and Consumers' Working Party

SAWP: Scientific Advice Working Party

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What added value for patients representatives in EMA?

- Bring a unique and critical input, the "patient perspective", based on real-life experience of the disease and it's current therapeutic environmental;
- Identifying patients with experience of the disease when necessary, on behalf of those directly affected by regulatory decisions;
- Contributing to patient information and communication related to medicines to ensure their stakeholders can access useful and understandable information;
- Increasing **transparency**, building **confidence** and **trust** in the regulatory process;
- Disseminating committees' outcomes when they become public to other patients and patients' organisations;
- Advising and supporting regulators in its dialogue with industry and other stakeholders when identifying areas of medical need for target research

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Working with Committees: not an easy ride

- A patient representative is to be valued and listened to as an equal in any debate;

- A patient representative should offer informed constructive challenge and interventions;

- A patient representative is expected to draw on sources of information or support outside the Committee and bring them coherently into the discussion;

- A patient representative should be able to initiate action, not merely respond to issues, including identifying topics for the Committee to consider.

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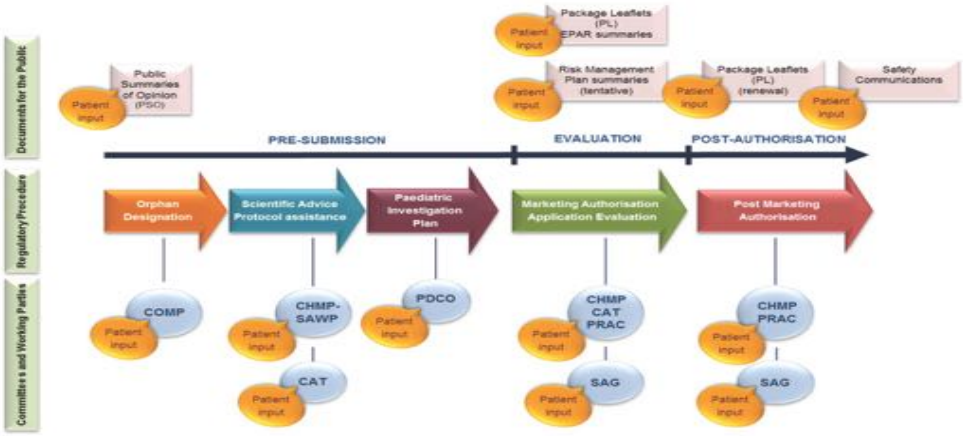
Overview of patient involvement along the medicines lifecycle at EMA



COMP: Committee for Orphan Medicinal Products
PDCO: Paediatric Committee
PRAC: Pharmacovigilance Risk Assessment Committee
CHMP: Committee for Medicinal Products for Human Use
SAWP: Scientific Advice Working Party
CAT: Committee for Advanced Therapies
SAG: Scientific Advisory Group
EPAR: European Public Assessment Report

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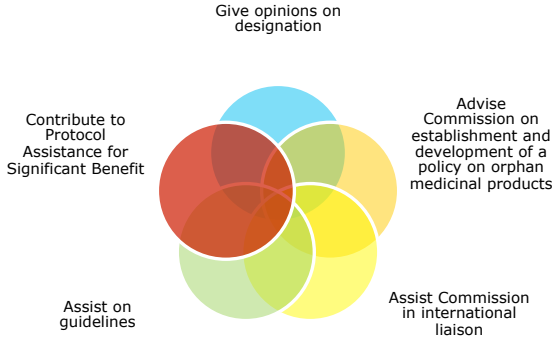
Current EMA/COMP activities in the orphan landscape
COMP mission and responsibilities



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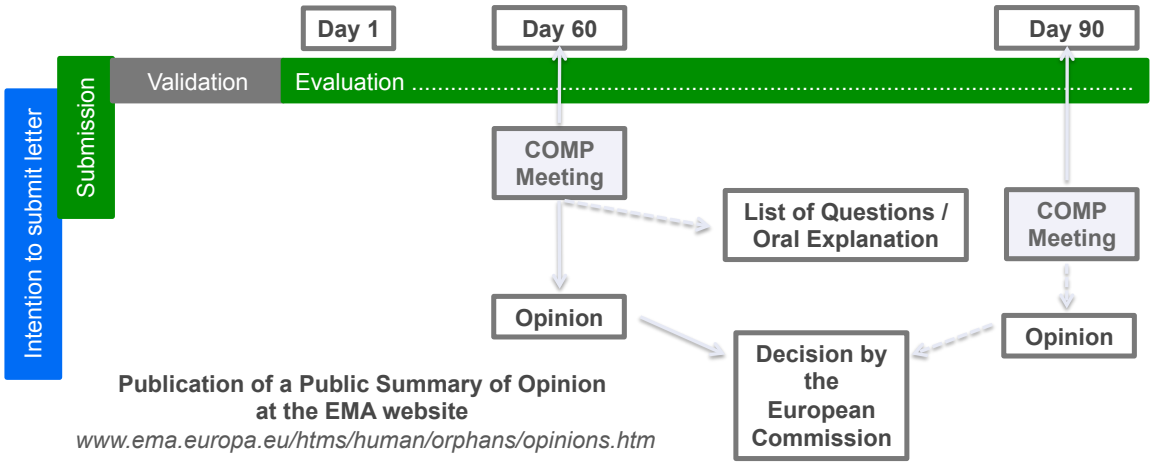
The designation process in the EU



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The Advisory Role of the COMP

- Regular exchange of information with EC to identify high level research needs
- Access to information on development
- Regulators have direct contact experience with successes and failures
- Direct access to a wealth of information
- International collaboration between regulators (USA, Japan, Canada)

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Translation of regulatory experience to guidance

The scientific and regulatory experience from designations, protocol assistance and marketing authorisations gives us valuable information to identify bottle necks, research needs

Analysing the reasons why there continue to be **gaps in the development of orphan medicines**

- negative outcome of an MAA
- withdrawn and negative applications for designation
- rare diseases where we see no or very little development

To be used to reduce the gaps for the benefit of the public health

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International collaboration

Rationale and background:

- Rare diseases share common needs / challenges in western world
- Orphan drugs are developed at a global level
- Advantages of pooling incentives

<u>Confidentiality arrangements</u>

- EU - FDA
- EU - Japan
- EU - Canada
- EU - Australia

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International collaboration (II)

International liaison officers, exchange of staff

Clusters for therapeutic area and for orphan medicines

Collaboration with the FDA at the stage of designation, development (parallel EMA/FDA PA), post-authorisation

For orphan designation: communication-collaboration during assessment

- Analysis of divergent opinions
- Sharing of information in real time

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International collaboration (III)

Harmonisation

- Regulation permitting (!)

Administrative simplification

- Facts (US-EU):
  - common application form
  - single submission of annual reports

Designation increasingly done in parallel

- App 60% of designations in parallel EMA/FDA
- 22% in parallel with Japan

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COMP responsibilities

"Dreamworks"

COMP

CHMP

Idea

Hypothesis

Assumption or viable hypothesis

Proof / Evidence

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Designation criterion

RARITY (prevalence) / RETURN OF INVESTMENT

- Medical condition affecting not more than 5 in 10,000 in the EU (around 250,000 people)
- Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

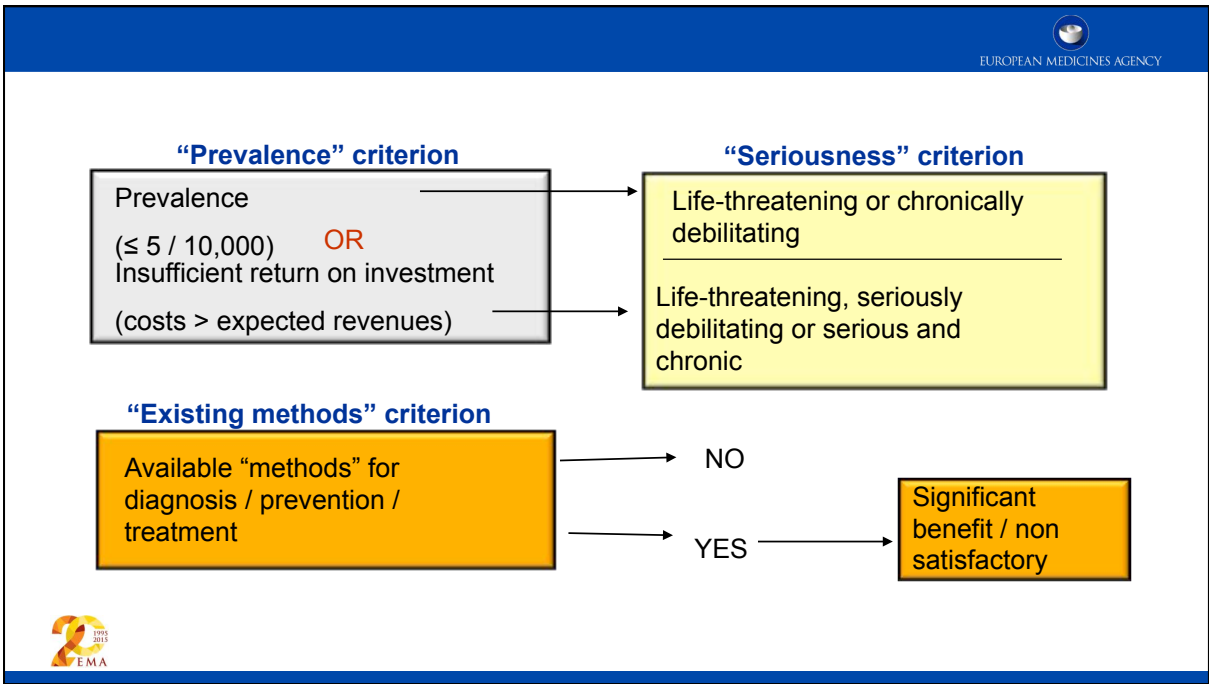
SERIOUSNESS

- Life –threatening or chronically debilitating

ALTERNATIVE METHODS AUTHORISED

EXCLUSIVE for EU

- If satisfactory method exist the sponsor should establish that the product will be of significant benefit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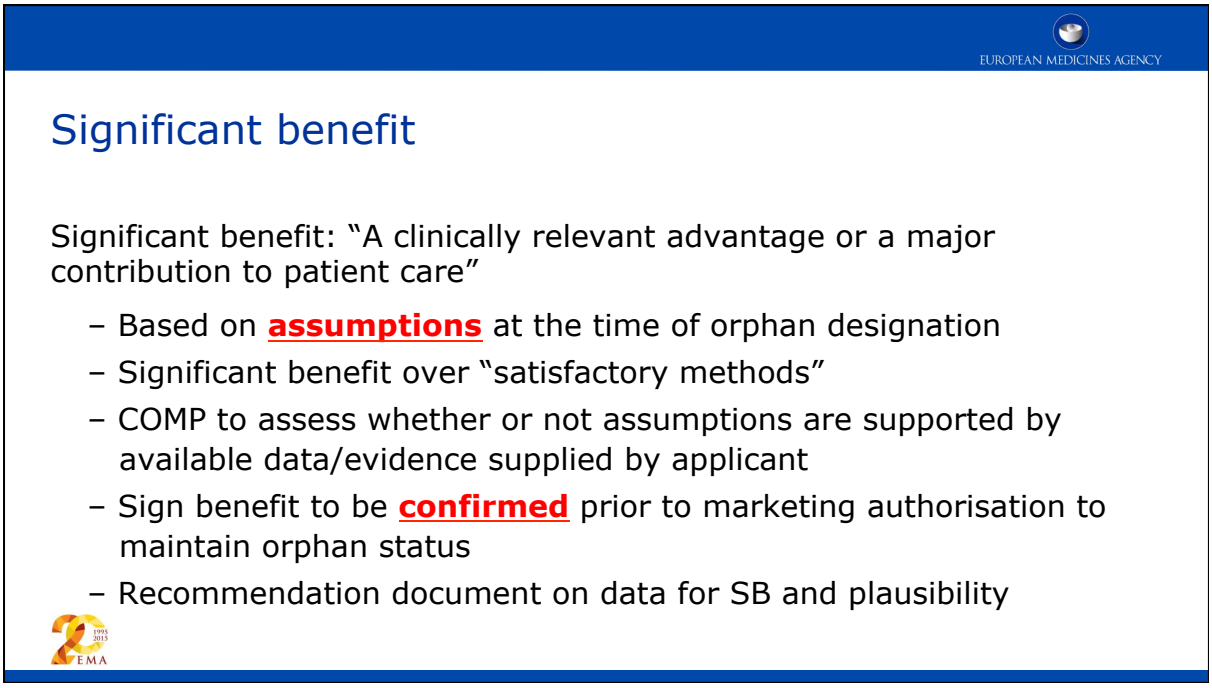
"Prevalence" criterion
Prevalence
(≤ 5 / 10,000)
OR
Insufficient return on investment
(costs > expected revenues)
"Seriousness" criterion
Life-threatening or chronically debilitating
Life-threatening, seriously debilitating or serious and chronic
"Existing methods" criterion
Available "methods" for diagnosis / prevention / treatment
NO
YES
Significant benefit / non satisfactory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Significant benefit
Significant benefit: "A clinically relevant advantage or a major contribution to patient care"
– Based on assumptions at the time of orphan designation
– Significant benefit over "satisfactory methods"
– COMP to assess whether or not assumptions are supported by available data/evidence supplied by applicant
– Sign benefit to be confirmed prior to marketing authorisation to maintain orphan status
– Recommendation document on data for SB and plausibility

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Examples assumption for significant benefit

Clinically relevant advantage

- Drug has a new mechanism of action: clinically relevant advantage to be justified/ demonstrated
- Opens possibilities for drug combination
- Alternative therapeutic option
- "complementary / better" safety profile

Major contribution to patient care

- Improvement quality of life (e.g. alternative to dietary restrictions)
- More "convenient" administration route
- Age adjusted formulation

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Protocol Assistance - Procedure

40 or 70-day procedure (maximum)

- Pre-submission meeting highly recommended
- Discussion meetings with SAWP (in 50%)
  - Major disagreement
  - Need for additional information

Final advice letter adopted by CHMP and COMP (for SB issues)

COMP involved if issues on significant benefit

Possibility of EMEA-FDA parallel advice

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Critical issues about SA/PA

Sponsor

Ask question if

- Deviation from guidelines
- Uncertainty

Ask at the appropriate time

- Early
- Transition

Come back if necessary

Follow the advice !!

Agency

Involve experts if necessary (including patients) … conflicts of interest!

Feasibility

Flexibility (as much as possible)

Clear and comprehensive

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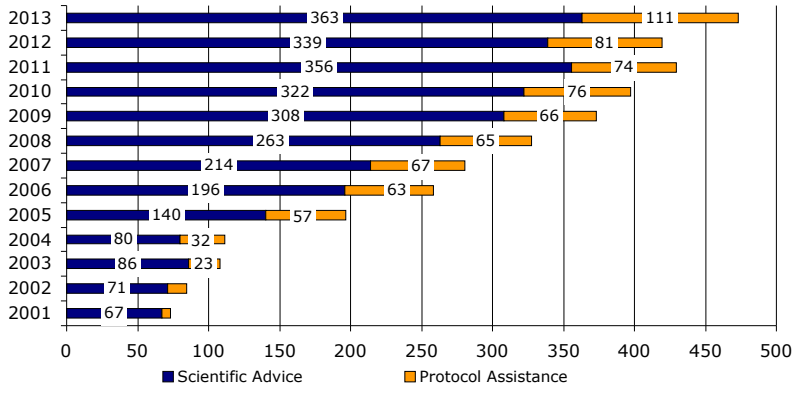
Increasing use of protocol assistance for orphan drugs under development



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Scientific-advice and protocol-assistance requests received

	2011	2012	2013	2014
Scientific-advice and follow-up requests	354	339	365	405
Protocol-assistance and follow-up requests	79	81	108	113
Of the above requests:				
Requests for parallel SA and protocol assistance with HTA			7	11
Requests for parallel SA and protocol assistance with international regulators			8	2
Requests for qualification of novel methodologies				22
Post-authorisation scientific advice requests			116	122

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COMP

- Designates at any stage of development
- Resubmission is user friendly
- *Occasionally might encourage dreams*

"Gate opener"

CHMP

- Interrogative
- Adversarial
- If in doubt, negative
- Prudent and cautious
- Quality, Safety and Efficacy

"Gate keeper"

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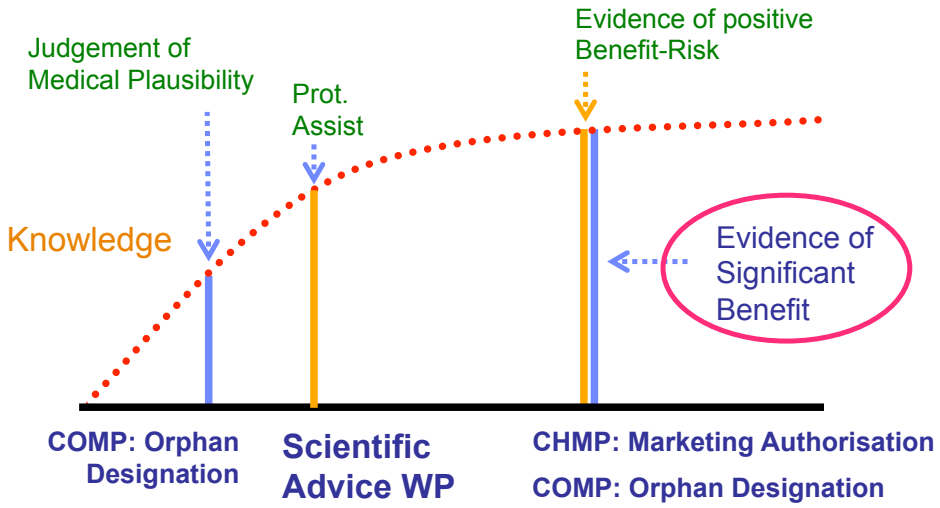
COMP and CHMP roles



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Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only via centralised procedure

CHMP responsible for assessment

- Authorisation within designated condition
- More than one designation possible per product (independent incentives)

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Specific requirements MAA (I)

Assessment of similarity (WHEN ORPHAN IS ON MARKET)

- Applies if other orphan medicines authorised for same designated condition
- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication ("significant overlap of populations"?)
- Assessment by CHMP competent working party
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision
- Proactive publication on going procedures

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Specific requirements MAA (II)

Maintenance designation criteria

- Report to orphan medicines section
  - At time of submission MA
  - Possible to update
- Need to address all designation criteria
- Standard set at time of authorisation
- Assessment by COMP; opinion after MA opinion by CHMP

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"Rejected applications have more Major Objections at D120 LoQ and a lower degree of randomized, blinded, controlled studies than the MA granted applications."

"This is in-line with published studies which have found that demonstrating convincing evidence on clinically relevant end-points is correlated with success of orphan medicinal products."

Putzeist *et al*. Drug Discovery Today 2011
Determinants for successful marketing authorisation of orphan medicinal products in the EU

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Examples of authorised products not showing SB

Product	SB at orphan designation	At marketing authorisation
Ruconest (R. Human C1 inhibitor) MA 28/10/2010 Treatment of angioedema	Availability	Berinert (plasma derived C1 inhibitor) approved in 22 member states through mutual recognition
Votrient (Pazopanib) MA 14/06/2010 Treatment of renal cell carcinoma	New mechanism of action and improved efficacy (preclinical data)	Pazopanib was unable to show a relevant clinical advantage compared to sunitinib or sorafenib
Teysuno (Tegafur, gimeracil, oteracil) MA 14/03/2011 Treatment of gastric cancer	Improved effect	Teysuno+cisplatin not shown to be superior to 5-FU+cisplatin. Improved safety claimed could not be supported by data
Cinryze (Human C1 inhibitor) MA 15/06/2011 Treatment of angioedema	Availability and longer duration	Availability; Berinert see above. The pharmacokinetic characteristics has not been translated to a relevant clinical advantage
Ixario		Prevalence criteria re-evaluated at marketing authorisation

55

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Can regulators foster development?

Principal role is regulating medicines

- Can regulators be indifferent to failures or lack of development?

Need to stay away from being directly involved

- Data /results assessment, central to regulators, should be done independently
- Need to ensure there are no conflicts of interest

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Fostering orphan drug development

Medicines development

- Orphan designation and protocol assistance
- Scientific validation / guided development

Economic incentives

- Fee reductions and market exclusivity
- Economic viability

Support to research

- COMP advisory role to EC on policy for orphan medicines
- Knowledge "repository" and target identification – public regulatory intelligence

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Fee reductions

Annually EU allocated special fund to cover fee reductions (approx. 6 million Euro)

EMA has consistently kept maximum coverage for SMEs

Academia and SME responsible for 79% development of advanced therapies

Policy reviewed annually, needed revision in 2013 according to current budget

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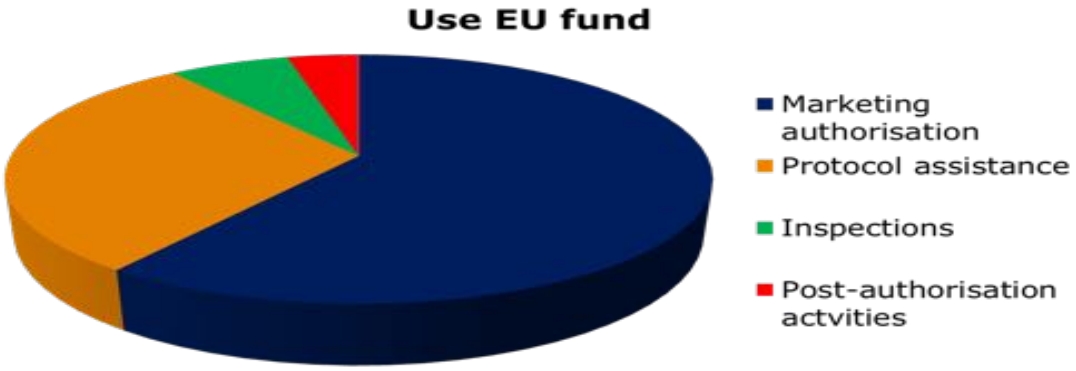
Allocation funds for fee reductions (2012)



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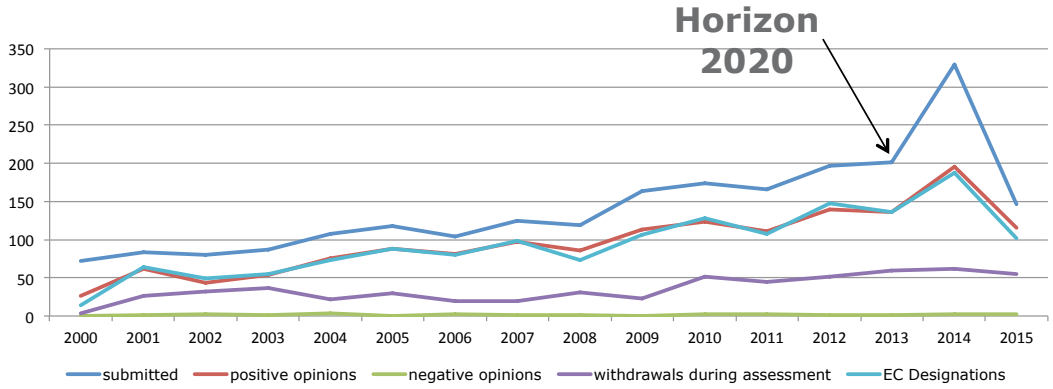
Status of Orphan Applications - July 2015



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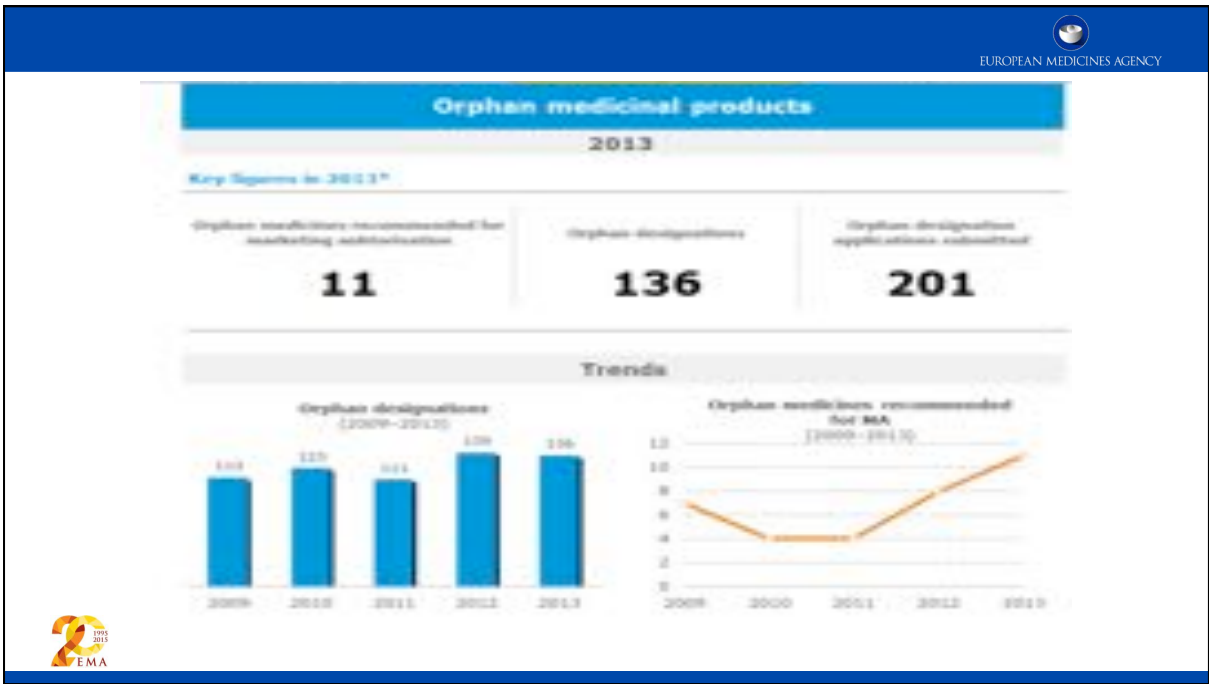
IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Objective 2020: 200 new therapies

Innovative Medicines Initiative



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Areas of growing interest and trends in OMP development

Eye diseases: e.g.Retinitis pigmentosa, Non-infectious uveitis, Leber's congenital amaurosis, Choroideremia, Stargardt's disease

Skin diseases: e.g. Epidermolysis bullosa, Congenital ichthyosis, Dyskeratosis congenita, Pemphigus;

Genetic a/o Metabolic disorders – continuing and rising

Conditions in prematurely born infants (e.g. Bronchopulmonary dysplasia, Respiratory Distress Syndrome, Retinopathy of prematurity)

Tropical diseases: Malaria, Leishmaniasis

'**The first orphan designation sparks the interest**' – clusters of applications for e.g. pulmonary arterial hypertension, hemophilias (A and B), amyloidosis, epidermolysis bullosa, Fragile X syndrome

New types of therapies - Gene therapies (one authorized so far)/ Stem cell therapies (mesenchymal etc.), cancer 'vaccines'

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The most frequently designated Orphan Conditions and MAs

Acute myeloid leukaemia	50	3	
Cystic fibrosis	49	4	
Glioma	**48**	**1 (Diagnostic)**	
Pancreatic carcinoma	**39**	**0**	
Ovarian cancer	30	2	
Multiple myeloma	27	3	
Chronic lymphoblastic leukaemia	24	3	
Duchenne's muscular dystrophy	24	1	
Acute lymphoblastic leukaemia	22	4	
Hepatocellular carcinoma	22	1	
Pulmonary arterial hypertension	17	7	
Amyotrophic lateral sclerosis	16	0	
Idiopathic pulmonary fibrosis	16	1	
Retinitis pigmentosa	15	0	
Cutaneous T-cell lymphoma	14	0	
Graft versus Host Disease	14	0	
Renal cell carcinoma (Prevalence>5/10 000 since 2011)	**22**	**4**	(Update 01/01/2015)

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Evolution witnessed during the last 15 years
types of provision providing the right incentives to company

The orphan designation and review procedures nowadays run smoothly

Initially – market exclusivity was the main incentive –

now – protocol assistance (PA)

PA procedure well adapted to rare conditions, small companies etc.

Parallel advice

Marketing Authorization (MA) procedures: Conditional Approval, Approval under Exceptional Circumstances, Accelerated Assessment

Adaptive pathways

So – the incentives provided by the Orphan Regulation to companies seem to work…

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'Proposals to promote drug innovation often focus on providing greater incentives for drug manufacturers by extending patent terms or reducing regulatory barriers to FDA approval, *instead of focusing on increasing support for the research that is so often the source of innovative therapeutic ideas*.'

From: Kesselheim A et al, 'The Roles Of Academia, Rare Diseases, And Repurposing In The Development Of The Most Transformative Drugs' (HEALTH AFFAIRS 34, NO. 2 (2015): 286–293)

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Status of Orphan Applications

	2000 2005	2006 2010	2011	2012	2013	2014	July 2015	Total
Applications submitted	548	686	166	197	201	329	146	2273
Positive COMP Opinions	348	500	111	139	136	196	116	1546
Negative COMP Opinions	8	6	2	1	1	2	2	22
EC Designations	343	485	107	148	136	187	102	1508
Withdrawals during assessment	150	144	45	52	60	62	55	568

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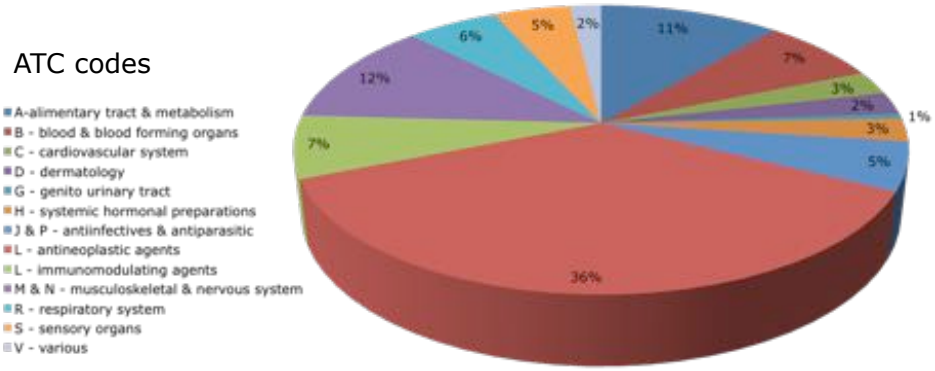
Distribution of Opinions by therapeutic area
from year 2000 – 2014
Total opinions 1430



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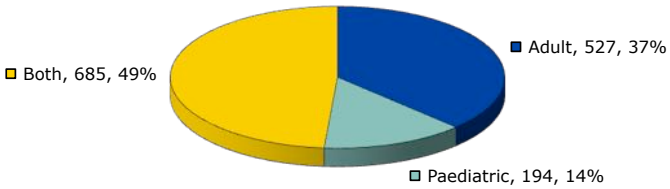
Adult/Paediatric Use
1406 designations up to 2014



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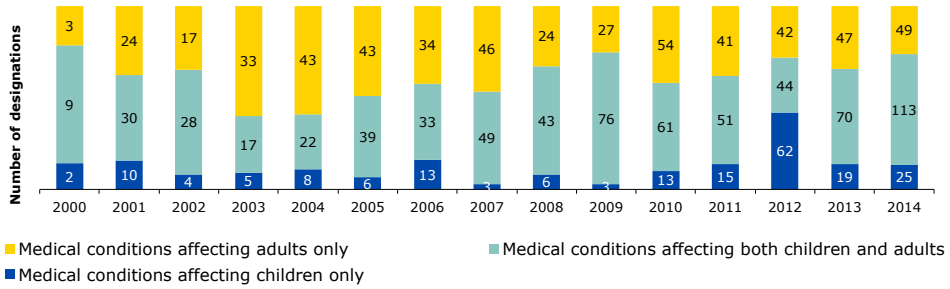
Adult/Paediatric Use

1406 designations up to 2014



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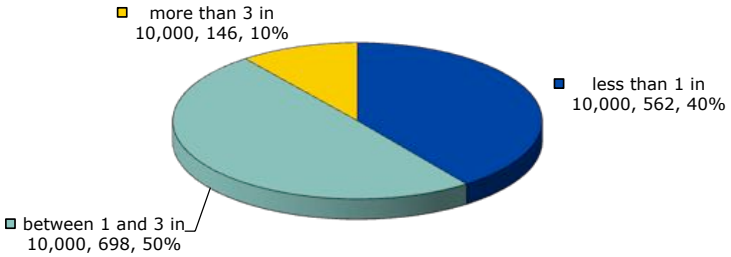
Prevalence Designated Conditions

1406 designations up to 2014



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Products Withdrawn from EC Register

- Orphan status withdrawn from Community Register of **orphan** medicinal products after authorisation at sponsor's initiative:

  Xyrem, Sutent, Afinitor, Ilaris, Revolade, Glivec (5 ext. of indication), Tracleer (ext. of indication)

- Products withdrawn from Community Register of medicinal products for **human** use at sponsor's initiative:

  Thelin (orphan status also withdrawn), Onsenal, Photobarr (orphan status also withdrawn), Rilonacept Regeneron

- Orphan status withdrawn from Community Register of **orphan** medicinal products after the **expiry of the market exclusivity period**

  Fabrazyme, Replagal, Glivec, Trisenox, Tracleer, Zavesca, Somavert, Carbaglu, Aldurazyme, Busilvex, Ventavis, Litak, Lysodren, Pedea, Wilzin, Prialt, Orfadin

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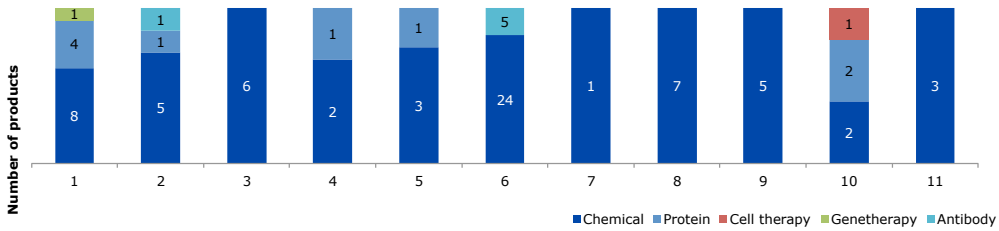
Indications and type of product excluding extension of indications/variations Period 2000- July 2015



Therapeutic area

A-alimentary tract & metabolism
B - blood & blood forming organs
C - cardiovascular system
H - systemic hormonal preparations
L - antineoplastic agents
L - immunomodulating agents
M & N - musculoskeletal & nervous system
R - respiratory system
V - various
J & P - antiinfectives & antiparasitic

83 authorisations including 4 withdrawals from the register of medicinal products human use

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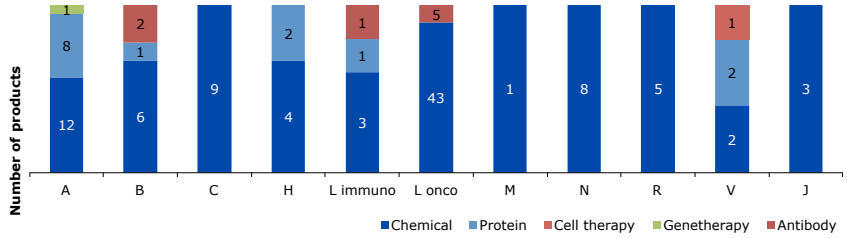
Indications and type of product including extension of indications Period 2000- July 2015



Therapeutic area

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V - various
J & P - antiinfectives & antiparasitic

121 products including the withdrawals from register of orphan medicinal products, register medicinal products human use and expired orphan status

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Status of Orphan Marketing Authorisations Applications: 105 granted

- Adopted positive opinion by CHMP awaiting decision: **8**
- On-going applications in review process: **27**
- Extensions of indication in review process: **1**
- Negative outcomes for orphan MAA
  - **51** withdrawn during evaluation, including **2** extensions
  - **4** withdrawn register human medicinal products
  - **13** withdrawn register orphan medicinal products after authorisation, including 7 extensions
  - **16** withdrawn register orphan medicinal products before authorisation, including 1 extensions
  - **11** refusals

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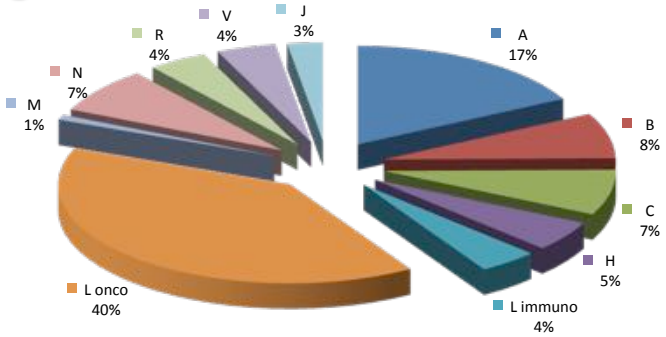
Distribution of Orphan MAA

105 granted to date* Period 2000-2014

A Alimentary tract and metabolism
B Haematology
C Cardiovascular system
H Systemic hormonal
J Antiinfectives for systemic use
L Immunology
L Antineoplastic
M Musculo-skeletal system
N Nervous system
R Respiratory system
V Various



Number of conditions: 85
(including extension of indications/variations)

* 5 withdrawn from the register of orphan medicinal products
4 withdrawn from register medicinal products human use
17 removed from register after expire of the market exclusivity period

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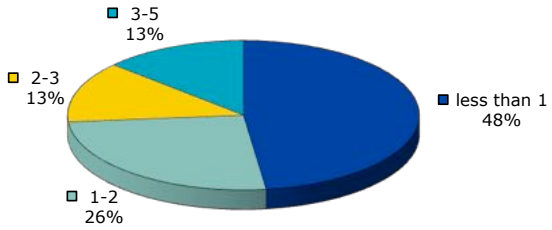
Prevalence Period 2000-2014

Prevalence per 10,000 - All orphan products
Including products later withdrawn by the sponsor and extension of indication



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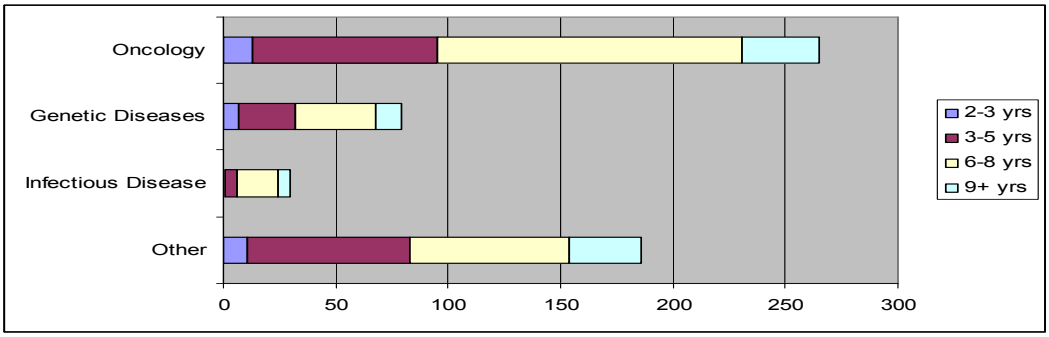
Future Projections / Estimates



Source: Castellani JJ. Orphans Drugs in Development for Rare Diseases. 2011, available at: www.phrma.org/sites/default/files/878/rarediseases2011.pdf

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Conclusions

- Orphan designation is centralised in the EU → Applications to be submitted to EMA and assessed by COMP; designations by European Commission
- Significant benefit exclusive to EU: justifications to support claims (even at early stage)
- Continued high interest in designations and increasing use of protocol assistance
- Many designated products in the MAA process
- Many rare diseases still no development, more diagnostics could benefit from the incentives.
- Changing classifications, similarity and significant benefit
- Active international collaboration
- Improve early dialogue to increase development success
- Continued support to research, SME and academic sponsors

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Committee of Orphan Medicinal Products

*There is no disease so **rare**, that it does not deserve attention*

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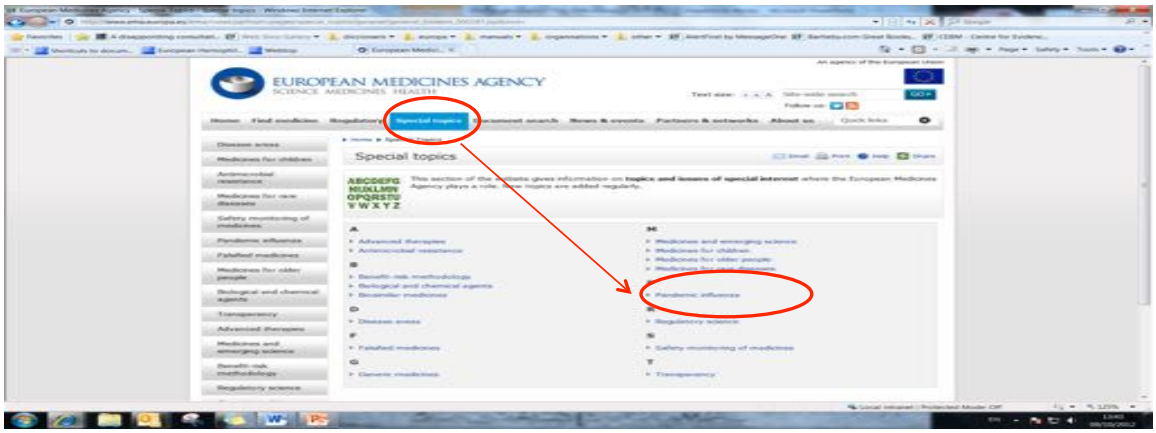
Where to have more information



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Where to have more information

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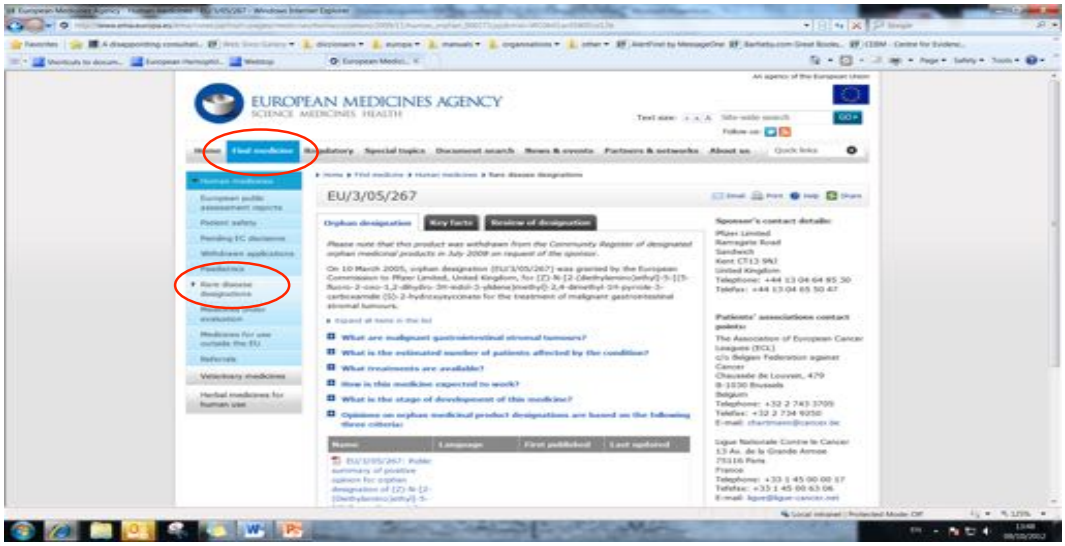

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Thank you for your attention

Further information

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Additional information

An agency of the European Union

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Authorised Orphan Medicines

for Therapeutic Groups

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Alimentary tract and metabolism

Bowel syndrome	Revestive
Cystinosis	Procysbi
Fabry disease	Replagal (orphan status expired 7/8/11) Fabrazyme (orphan status expired 7/8/11)
Familial lipoprotein lipase deficiency	Glybera
Gaucher disease	VPRIV, Zavesca (orphan status expired 21/11/12), Cerdelga
Glycogen Storage Disease	Myozyme
Hyperphenylalaninemia	Kuvan
Isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia	Carbaglu[1]
Homocystinuria	Cystadane
Mucopolysaccharidosis type I	Aldurazyme (orphan status expired 12/06/13)

[1]extension of indication/variation

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Alimentary tract and metabolism

Mucopolysaccharidosis type II	Elaprase
Mucopolysaccharidosis type IVA	Vimizim
Mucopolysaccharidosis type VI	Naglazyme
N-acetylglutamate synthetase deficiency	Carbaglu (orphan status expired 28/01/13)
Niemann-Pick type C disease	Zavesca[1]
Primary bile-acid synthesis	Orphacol, Cholic Acid FGK
Tyrosinaemia	Orfadin (orphan status expired 24/02/15)
Familial lipoprotein lipase deficiency	Glybera
Wilson's disease	Wilzin

[1]extension of indication/variation

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Systemic hormonal

Adrenal insufficiency	Plenadren
Acromegaly	Somavert (orphan status expired 15/11/12), Signifor
Cushing's disease	Signifor, Ketoconazole Lab HRA Pharma
Growth failure	Increlex

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Cardiovascular system

Angioedema	Firazyr
Patent ductus arteriosus	Pedea
Pulmonary arterial hypertension Thromboembolic pulmonary hypertension (CTEPH) and Pulmonary arterial hypertension (PAH)	Tracleer (orphan status expired 15/5/12), Ventavis (orphan status expired 18/09/13), Revatio, Thelin (withdrawn register medicinal products human use), Volibris, Opsumit Adempas

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Haemathology

Atypical haemolytic uremic syndrome	Soliris[1]
Chronic Iron overload due to blood transfusions	Exjade
Hepatic veno-occlusive disease	Defitelio
Idiopathic thrombocytopenic purpura	Revolade (withdrawn register of orphan medicinal products)
Paroxysmal nocturnal hemoglobinuria	Soliris
Post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis	Jakavi
Primary myelofibrosis	Jakavi

[1]extension of indication/variation

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Haemathology

Sickle cell syndrome	Siklos
Thrombocythaemia	Xagrid
Thrombocytopenia	Nplate

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Immunology and immunomodulatory

Cryopirin-associated periodic syndromes	Ilaris (withdrawn register of orphan medicinal products), Rilonacept
Multiple myeloma	Revlimid, Thalidomide Pharmion 50mg hard capsules, Pomalidomide Celgene

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Antineoplastic

Acute lymphoblastic leukaemia (ALL)	Evoltra, Glivec[1] (withdrawn register of orphan medicinal products), Sprycel, Atriance, Xaluprine, Iclusig
Acute myeloid leukaemia (AML)	Vidaza, Ceplene, Dacogen
Acute promyelocytic leukaemia	Trisenox (orphan status expired 7/3/12)
Adrenal cortical carcinoma	Lysodren
Anaplastic large cell lymphoma	Adcetris
Barrett's oesophagus	Photobarr (withdrawn register medicinal products human use)
Castleman's disease	Sylvant
Chronic lymphocytic leukaemia (CLL)	Arzerra, Gazyvaro, Imbruvica

[1]extension of indication/variation

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Antineoplastic

Chronic myeloid leukaemia (CML), Chronic myelogenous leukaemia, Chronic myelomonocytic leukaemia (CMML)	Glivec (expired 12/11/11), Sprycel, Tasigna, Vidaza, Bosulif, Iclusig
Dermatofibrosarcoma protuberans	Glivec[1] (withdrawn register of orphan medicinal products)
Familial Adenomatous Polyposis	Onsenal (withdrawn register medicinal products human use)
Gastric cancer	Cyramza
Gastro intestinal stromal tumours	Sutent (withdrawn register of orphan medicinal products), Glivec[1] (withdrawn register of orphan medicinal products)
Haematopoietic progenitor cell transplantation	Busilvex (orphan status expired 11/07/13), Tepadina

[1]extension of indication/variation

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Antineoplastic

Hairy cell leukaemia	Litak
Hepatocellular carcinoma	Nexavar[1]
Hypereosinophilic syndrome (HES/CEL)	Glivec[1] (withdrawn register of orphan medicinal products)
Hodgkin lymphoma	Adcetris
Mantel cell lymphoma	Torisel[1], Imbruvica
(Medullary) thyroid carcinoma (Differentiated) thyroid carcinoma	Cometriq Nexavar[1]
Myelodysplastic syndromes (MDS)	Vidaza, Glivec[1] (withdrawn register of orphan medicinal products), Revlimid[1]
Osteosarcoma	Mepact

[1]extension of indication/variation

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Antineoplastic

Ovarian cancer	Yondelis[1] , Lynparza
Renal cell carcinoma	Torisel, Afinitor (withdrawn register of orphan medicinal products), Sutent (withdrawn register of orphan medicinal products), Nexavar
Systemic sclerosis	Tracleer[1]
Soft tissue sarcoma	Yondelis
Subpendymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)	Votubia
Thyroid cancer	Lenvima
T-cell lymphoblastic lymphoma (T-LBL)	Atriance

[1]extension of indication/variation

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Antineoplastic

Visualisation of malignant tissue during surgery for malignant glioma	Gliolan
Waldenström Macroglobulinaemia (lymphoplasmacytic lymphoma)	Imbruvica[1]

[1]extension of indication/variation

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Musculo-skeletal system

Duchenne muscular dystrophy	Translarna

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Nervous system

Apnoea	Peyona
Chronic pain requiring intrathecal analgesia	Prialt (orphan status expired 24/02/15)
Epilepsy	Diacomit (myoclonic epilepsy in infancy) Inovelon
Lambert-Eaton Myasthenic Syndrome	Firdapse
Narcolepsy	Xyrem (withdrawn register of orphan medicinal products)
Non-24-Hour Sleep-Wake Disorder (Non-24) in the totally blind	Hetlioz
Transthyretin amyloidosis in patients with symptomatic polyneuropathy	Vyndaqel

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Respiratory system

Cystic fibrosis	Cayston, TOBI Podhaler, Bronchitol, Kalydeco
Idiopathic pulmonary fibrosis	Esbriet, Ofev

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Antiinfective, antiparasitic

Tuberculosis	Sirturo, Deltyba, Para-aminosalicylic acid Lucane

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Various

Anthracycline extravasation	Savene
Deep partial- and full-thickness thermal burns	Nexobrid
Stem cell transplantation	Mozobil
Errythropoietic protoporphyria	Scenesse
Treatment of limbal stem cell deficiency	Holoclar

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