EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Orphan Medicinal Products in the European centralised procedure – Current Marketing Authorisations for Gaucher Disease

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Overview

- Orphan designation and centralised procedure
- Submission and evaluation of a marketing authorisation application for an orphan medicinal products
- Authorised treatments in the area of Gaucher disease
- Paediatric data for authorised Gaucher treatments

Eligibility of orphan products

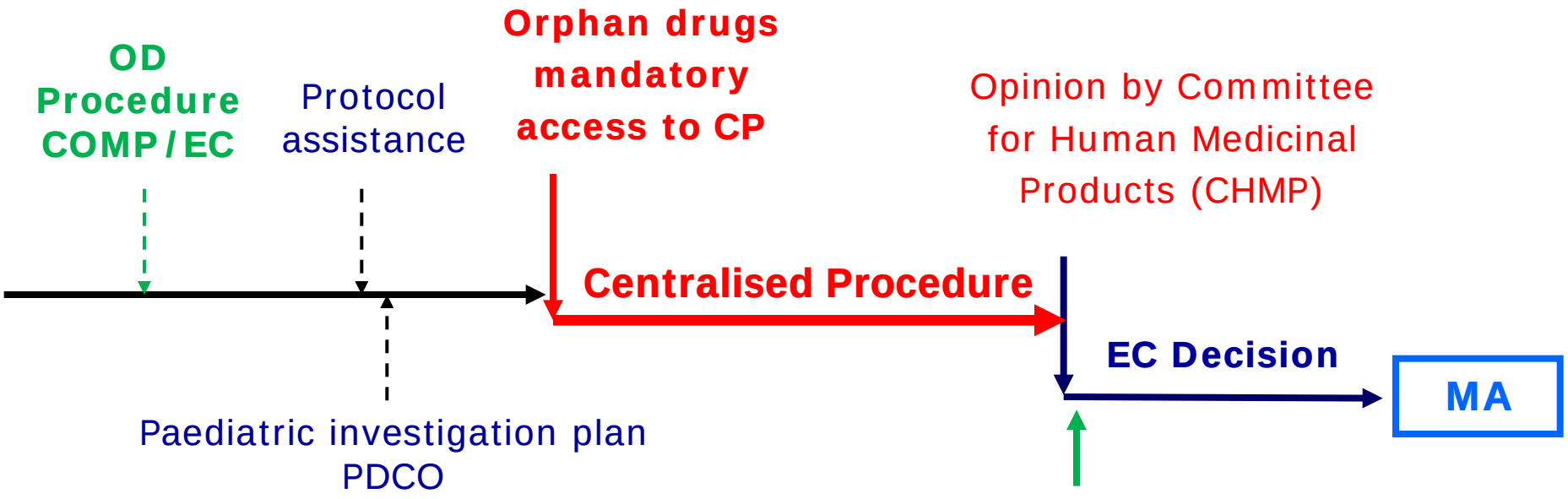
Centralised procedure - mandatory for all orphan medicinal products

Regulation (EC) 726/2004

Article 3(1)
*"1. No medicinal product appearing in the **Annex** may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation."*

ANNEX
*"Medicinal products that are designated as **orphan medicinal products** pursuant to Regulation (EC) No 141/2000."*

Centralised procedure and orphan medicinal products



Orphan incentives

- **Fee reductions**
- **Protocol assistance**
- **Inventory of EU Community and Member State incentives**
- **Market exclusivity**

OD: Orphan Designation

Market exclusivity

"...the Community and the Member States shall not, for a period of **10 years**, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, **for the same therapeutic indication, in respect of a similar medicinal product.**"*

Three derogation options:

(a) the holder of the MA for the original orphan medicinal product has given **consent** to the second applicant, or

(b) the holder of the MA for the original orphan medicinal product is **unable to supply** sufficient quantities of the medicinal product, or

(c) the second applicant can establish that the second medicinal product is safer, more effective or otherwise **clinically superior**.

*** REGULATION (EC) No 141/2000**

Submission

- Claimed indication is within orphan condition
- Applicant is the orphan designation holder
- Similarity report for all new applications for an indication, which is the same/overlaps with an authorised orphan medicinal product
- Report on maintenance of the orphan designation criteria

Communication to public (I)

Orphan drug designation by the COPM:
Register of designated Orphan Medicinal Products (by number):
http://ec.europa.eu/health/documents/community-register/html/orphreg.htm

Initiation of the evaluation of an MAA for (an orphan) medicinal product by the CHMP:

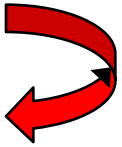
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000349.jsp&mid=WC0b01ac05805083eb

Communication to public (II)

After the granting of the CHMP scientific opinion and during the decision making process:

-Preparation of the European Public Assessment Report (EPAR)

-Preparation of the Report on Re-examination of OD



Published on the EMA website

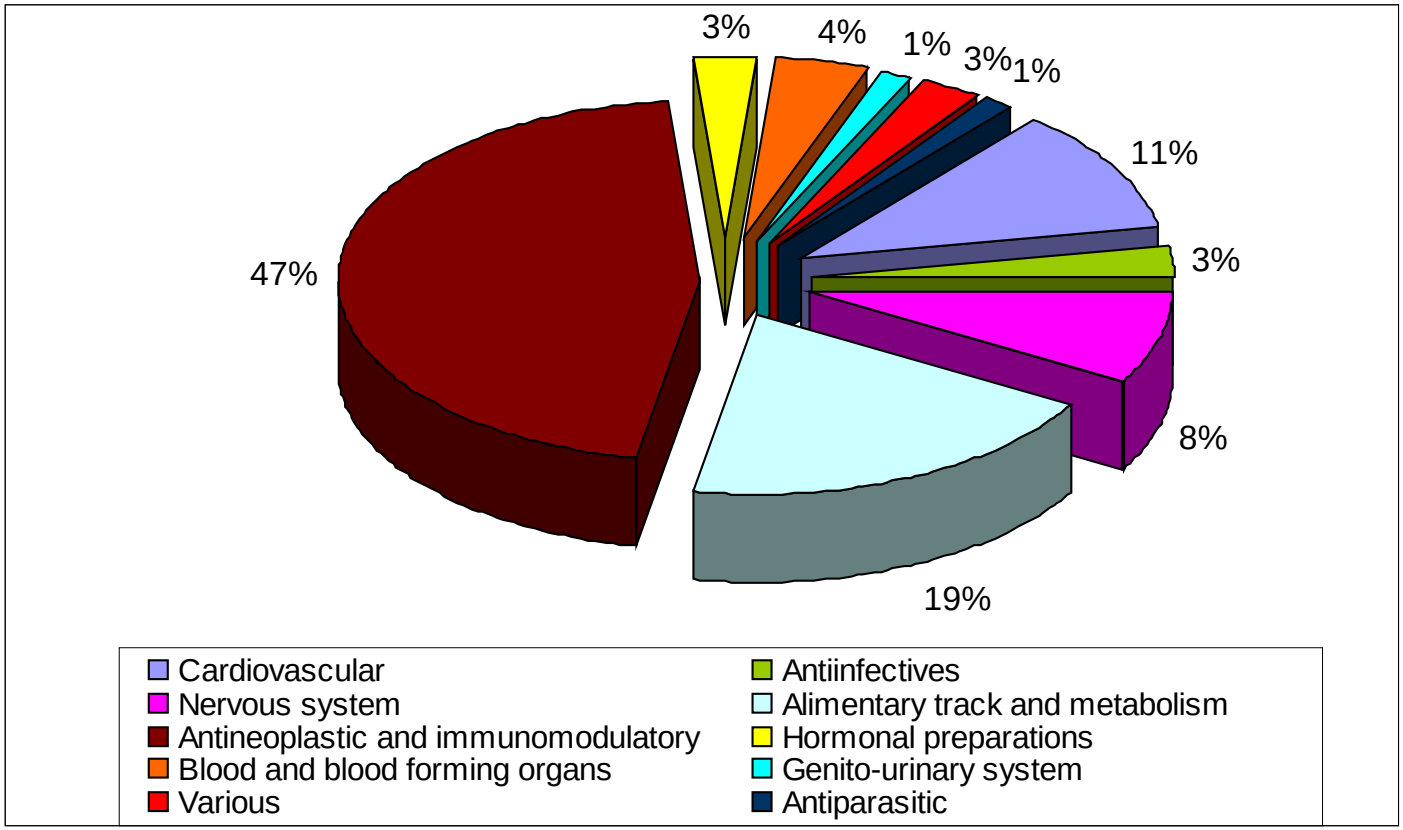
Example: Vpriv (velaglucerase alfa), EU Commission Decision, 26 Aug 2010

1.1.1. For new centralised dossiers orphan medicinal products

The applicant Shire Pharmaceuticals Ireland Ltd. submitted on 30 October 2009 an application for Marketing Authorisation to the European Medicines Agency through the centralised procedure for VPRIV, which was designated as an orphan medicinal product EU/3/10/752 on 09 June 2010. VPRIV was designated as an orphan medicinal product in the following indication: Treatment of Gaucher disease. The calculated prevalence of this condition was 0.3 in 10,000 persons EU population.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of VPRIV as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

Orphan MAAs with positive outcome by therapeutic area*



**data based on ATC code, positive CHMP opinion till June 2011*

Authorised Gaucher disease treatments

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Product	OD granted	Condition	Marketing Authorisation
Cerezyme (imiglucerase)	N/A	N/A	17 November 1997
Indication (MA)	**Applied for**	**Approved**	**Current**
	Cerezyme is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Type I Gaucher disease and who exhibit clinical manifestations of the disease.	As applied for	Cerezyme is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic **(Type 1)** or chronic neuronopathic **(Type 3)** Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.
Vpriv (velaglucerase alfa)	6 June 2010	Gaucher disease	26 August 2010
Indication (MA)	**Applied for**	**Approved**	**Current**
	Long-term enzyme replacement therapy (ERT) **for paediatric and adult patients** with type 1 Gaucher disease.	Long-term enzyme replacement therapy (ERT) **in patients** with **type 1 Gaucher** disease.	As approved
Zavesca (miglustat)	18 October 2000 16 December 2006	Gaucher disease Niemann-Pick disease type C	20 November 2002 26 January 2009
Indication (MA)	**Applied for**	**Approved**	**Current**
	Oral treatment of type 1 Gaucher disease.	Oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.	• 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. • Treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.

Cerezyme

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Indication:

For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease*

**Originally approved only in GD type 1. In 2003 - extension of indication to GD type 3 based on literature review, International Collaborative Gaucher Group Registry; large portion of children ≤ 17 years).*

Posology (initial dose 60 U/kg every two weeks):

...No dose adjustment is necessary for the paediatric population.

The efficacy of Cerezyme on neurological symptoms of chronic neuronopathic Gaucher patients has not been established and no special dosage regimen can be recommended for these manifestations.

Clinical data in SmPC:

... In children, Cerezyme has been shown to enable normal pubertal development, and to induce catch-up growth, leading to normal height and bone mineral density in adulthood.

- based on postmarketing data

Vpriv I

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Indication:

Long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease

Posology (60 U/kg every two weeks) :

21% patients during studies were in the paediatric and adolescent age range (4 to ≤17 years)… safety and efficacy profiles were similar.

Clinical data in SmPC:

…studies allowed the inclusion of patients 2 years and older… safety and efficacy profiles are expected to be similar down to the age of 2 years. However, no data are available for children under the age of 4 years.

PIP agreed: waiver and deferral → data are awaited

Vpriv II

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Pivotal comparative phase III trial HGT-GCB-039 in the initial MAA:

Primary efficacy endpoint - difference in Hgb mean change from baseline to week 41 between groups

Secondary endpoints - differences in mean and percent changes from baseline in platelet count, liver and spleen volumes measured by MRI, plasma chitotriosidase activity, plasma CCL18 levels, and in time to response for Hgb ≥1 g/dL from baseline.

	Vpriv	Cerezyme
AGE		
0-4 years	0	4
5-17 years	4	1
≥18 years	13	12
Total	34	

→ For primary, secondary and other efficacy parameters- no firm conclusion, but suggestion of data consistency between children and adults. No safety signal specific to children.

Elelyso

Taliglucerase alfa

- **Expected to be used for the long-term treatment of patients with type 1 Gaucher disease**
- **MAA submitted to the EMA/CHMP with adequate similarity report**
  - → Elelyso was found to be similar to Vpriv
- **Derogation report submitted to EMA/CHMP**
  - Claims of clinical superiority and inability to supply sufficient amount of Vpriv
  - → Claims of derogation not fulfilled
- **The CHMP could not recommend the granting of the MA for Elelyso (awaiting CD)**

Paediatric development of Elelyso – in EudraCT database:

PB06005: A double-blind, randomised efficacy and safety study of taliglucerase alfa enzyme replacement therapy in children and adolescents with Gaucher disease (non-neuronopathic and chronic neuronopathic)

2 to<18 years, median percentage and the interquartile range for change from baseline in haemoglobin

In summary…

- **Prior to submission – orphan designation (COMP), PIP (PDCO)**
- **Submission – automatic access of orphan drugs into centralised procedure**
- **Clinical package –> evaluation -> indication granted by the CHMP**
- **Specific evaluation of paediatric population**
- **Guidance for prescriber about the use of the product in paediatric population (SmPC)**

THANK YOU FOR YOUR ATTENTION

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