3 March 2015
EMA/COMP/472719/2007 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for the treatment of Gaucher disease

First publication	1 July 2008
Rev.1: information about Marketing Authorisation	3 March 2015

Disclaimer

Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.

On 4 December 2007, orphan designation (EU/3/07/514) was granted by the European Commission to Genzyme Europe BV, Netherlands, for (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for the treatment of Gaucher disease.

What is Gaucher Disease?

Gaucher disease is characterized by the accumulation of specific chemical substances (glucocerebrosides) in several cells (macrophages and monocytes) that are localized throughout the body, but particularly in the spleen, liver and bone marrow. The disorder results from the decreased activity of an enzyme (a protein that stimulates a chemical reaction in the body), called glucocerebrosidase; this enzyme destroys the glucocerebrosides. Since glucocerebrosides are not destroyed, they progressively accumulate in the cells. The disorder has a genetic origin, so it is caused by damage in a gene that carries the information necessary for the production of the enzyme. Usually both parents are healthy carriers of a single copy of the damaged gene. To develop the disease, two damaged copies must be present in the same individual (this is called autosomal recessive inheritance). The severity of Gaucher disease is extremely variable; some patients show with virtually all the complications of Gaucher disease during childhood, while others remain asymptomatic for more than 70 years.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Gaucher disease has traditionally been divided into the following 3 clinical subtypes, according to the absence or presence of damage to the nerves and its progression:

- Type 1 - Nonneuronopathic form (the most common and less severe form);
- Type 2 - Acute neuronopathic form (the most severe form, usually diagnosed shortly after birth);
- Type 3 - Chronic neuronopathic form (a form of intermediate severity between Type 1 and Type 2).

However, some cases do not precisely fit into one of these categories. Gaucher disease can be life-threatening (Type 2 and 3) or chronically debilitating (Type 1).

What is the estimated number of patients affected by the condition?

At the time of designation, Gaucher disease affected approximately 0.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 15,000 people[*], and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of the application for orphan designation, two medicinal products were authorized in the European Union for the treatment of Gaucher syndrome, miglustat (Zavesca, given orally) and imiglucerase (Cerezyme, given intravenously). Given its different mechanism of action, (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt may be of potential significant benefit over the currently authorised medicinal products. This assumption will have to be confirmed at the time of marketing authorisation, and this will be necessary to maintain the orphan status.

How is this medicine expected to work?

(1R,2R)-Octanoic acid[2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt blocks the function of an enzyme called glucosylceramide synthase. This enzyme helps to build the substance that accumulates in Gaucher disease (the glucocerebrosides, which then cannot be eliminated because of the genetic defect in the enzyme that destroys them). Thus, by blocking the action of glucosylceramide synthase, the levels of glucocerebrosides in the body are reduced and its accumulation should also be reduced.

What is the stage of development of this medicine?

The effects of the medicinal product were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with Gaucher disease were ongoing.

The medicinal product was not authorised anywhere in the world for Gaucher disease, or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

[*]Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 27), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 500,300,000 (Eurostat 2007).

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 October 2007 recommending the granting of this designation.

Update: (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt, eliglustat (Cerdelga) has been authorised in the EU since 19 January 2015 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).

More information on Cerdelga can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

_____

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Genzyme Europe BV
Gooimeer 10
1411 DD Naarden
The Netherlands
Tel. +31 35 699 1499
Fax +31 35 699 1403
Email: eumedinfo@genzyme.com

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active Ingredient	Indication
English	(1R, 2R)-Octanoic acid [2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt	Treatment of Gaucher disease
Bulgarian	(1R, 2R)-октанова киселина [2-(2',3'-дихидро бензо [1,4] диоксин-6'-ил)-2-хидрокси-1-пиролидин-1-илметил-етил]-амид-L-тартарат	Лечението трябва да се провежда от лекари с запознати с терапията на болестта на Гоше
Czech	(1R, 2R)- oktankyselina [2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmetyl-etyl]-amid-L-sůl kyseliny vine	Léčba Gaucherovy choroby
Danish	(1R,2R)-octandinsyre [2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amid-vinsyresalt	Behandling af Gauchers sygdom
Dutch	(1R, 2R)-octaanzuur [2-(2',3'-dihydro-benzo [1,4] dioxine-6'-yl)-2-hydroxy-1-pyrrolidine-1-ylmethyl-ethyl]-amide-L-wijnsteenzuur-zout	Behandeling van de ziekte van Gaucher
Estonian	(1R, 2R)-kaprüülhape [2-(2',3'-dihüdrobenso[1,4-dioksiin-6'-üül)-2-hüdroksü-1-pürrolidiin-1-üülmetüületüül]-amiid-L-viinhappesool	Gaucher' tõve ravi
Finnish	(1R, 2R)-oktanohappo [2-(2',3'-dihydro-bentso [1,4] dioksiini-6'-yyli)-2-hydroksi-1-pyrrolidiini-1-ylmetyyli-etyyli]-amidi-L-viinihapposuola	Gaucherin taudin hoito
French	Sel de (1R,2R)-acide octanoïque[2-(2',3'-dihydro-benzo [1,4] dioxine-6'-yl)-2-hydroxy-1-pyrrolidine-1-ylméthyl-éthyl]-amide-L-acide tartrique	Traitement de la maladie de Gaucher
German	(1R,2R)-Oktansäure[2-(2',3'-dihydrobenzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amid-L-Tartrat	Behandlung der Gaucher-Krankheit
Greek	(1R,2R)-Οκτανοϊκό οξύ[2-(2',3'-διυδρο-βενζο [1,4] διοξίνη-6'-ύλιο)-2-υδροξυ-1-πυρρολιδίνη-1-υλμεθυλ-αιθυλ]-αμίδιο-L-άλας τρυγικού οξέος	Θεραπευτική αγωγή για την νόσο του Gaucher
Hungarian	(1R, 2R)-oktánsav [2-(2',3'-dihidro-benzo [1,4] dioxin-6'-il)-2-hidroxi-1-pirolidin-1-ilmetil-etil]-amid-L-tartarát	Gaucher-kór kezelése
Italian	acido(1R, 2R)- octanoico [2-(2',3'-diidro-benzo [1,4] diossin-6'-il)-2-idrossi-1-pirrolidin-1-il-metil-etil]-ammide-L- tartrato	Trattamento della malattia di Gaucher
Latvian	(1R, 2R)-oktānskābes [2-(2',3'-dihidrobenzo [1,4] dioksīna-6'-il)-2-hidroksi-1-pirolidīna-1-ilmetila-etila]-amīda-L-vīnskābes sāls	Gošē slimības ārstēšana

[1] At the time of designation

Language	Active Ingredient	Indication
Lithuanian	(1R, 2R)-oktano rūgštis [2-(2',3'-dihidro-benzo [1,4] dioksin-6'-il)-2-hidroksi-1-pirolidin-1-ilmetil-etil]-amido-L-tartaro rūgšties druska	Gošė ligos gydymas
Maltese	(1R, 2R)-Octanoic acid [2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt	Kura tal-marda ta' Gaucher
Polish	(1R, 2R)-kwas oktanowy [2-(2',3'-dihydro-benzo [1,4] dioksyno-6'-yl)-2-hydroksy-1-pirolidyno-1-ilmetylo-etyl]-amid soli kwasu L-winowego	Leczenie choroby Gaucher'a
Portuguese	ácido (1R, 2R)-octanóico, sal de ácido [2-(2',3'-di-hidro-benzo [1,4] dioxino-6'-il)-2-hidroxi-1-pirrolidina-1-ilmetil-etil]-amido-L-tartárico	Tratamento da doença de Gaucher
Romanian	Sare a acidului (1R, 2R)-acid octanoic [2-(2',3'-dihidro-benzo [1,4] dioxin-6'-il)-2-hidroxi-1-pirolidin-1-ilmetil-etil]-amido-L-tartaric	Tratamentul bolii Gaucher
Slovak	Soľ (1R, 2R)-kyselina oktánová[2-(2',3'-dihydrobenzo[1,4] dioxín-6'-yl)-2-hydroxy-1-pyrolidín-1-ylmetyletyl]-amid-L-kyseliny vínnej	Liečba Gaucherovej choroby
Slovenian	(1R, 2R)-Oktanojska kislina [2-(2',3'-dihidro-benzo [1,4] dioksin-6'-il)-2-hidroksi-1-pirrolidin-1-ilmetil-etil]-amid-L-sol vinske kisline	Zdravljenje Gaucherove bolezni
Spanish	ácido (1R, 2R)-octanoico, sal de ácido [2-(2',3'-di-hidro-benzo [1,4] dioxino-6'-il)-2-hidroxi-1-pirrolidina-1-ilmetil-etil]-amido-L-tartárico	Tratamiento de la enfermedad de Gaucher
Swedish	(1R, 2R)-kaprylsyra [2-(2',3'-dihydrobenso [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmetyl-etyl]-amid-L-vinsyresalt	Behandling av Gauchers sjukdom
Norwegian	(1R, 2R)-oktansyre [2-(2',3'-dihydrobenzo [1,4] dioksin-6'-yl)-2-hydroksy-1-pyrrolidin-1-ylmetyletyl]-amid-L-tartarsyresalt	Behandling av Gauchers sykdom
Icelandic	(1R, 2R)-Octanoik sýra [2-(2',3'-díhýdró-bensó [1,4] díoxín-6'-ýl)-2-hýdroxý-1-pýrrólídín-1-ýlmetýl-etýl]-amíð-L-vínsýru salt	Meðferð á Gauchersveiki