

European Medicines Agency Pre-authorisation Evaluation of Medicines for Human Use

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Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in June 2009 on request of the Sponsor.

Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of 4,5-dihydro-2-(2,4-dihydroxyphenyl)-4-methylthiazole-4(S)-carboxylic acid for the treatment of chronic iron overload requiring chelation therapy

On 12 December 2003, orphan designation (EU/3/03/180) was granted by the European Commission to Genzyme Europe BV, the Netherlands, for 4,5-dihydro-2-(2,4-dihydroxyphenyl)-4-methylthiazole-4(S)-carboxylic acid (GT56-252) for the treatment of chronic iron overload requiring chelation therapy

What is chronic iron overload requiring chelation therapy?

Chronic iron overload is a condition resulting from the inability to actively eliminate iron from the body. Chronic iron accumulation is mainly consecutive to either excess of intestinal absorption (hemochromatosis) or excess administration through repetitive blood transfusions (iron contained in transfused red blood cells). For example, patients presenting chronic anaemias (e.g. thalassemia, sickle cell anaemia) and who require repeated transfusions can be affected by iron overload. Chronic iron overload is a serious condition. Complications are related to iron deposits in tissues which can induce organ failure. This condition is life-threatening when the heart or the liver is affected.

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

At the time of designation, chronic iron overload requiring chelation therapy affected approximately 3 in 10,000 people in the European Union $(EU)^*$. This is equivalent to a total of around 120,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

Phlebotomy (blood removal by venipuncture) is the first-choice therapy for haemochromatosis, except when blood removal is impossible. For the latter patients, or for patients with transfusion-dependent anaemias, iron overload can be treated by administration of iron chelators. Medicinal products which chelate iron had been authorised in the Community at the time of submission of the application for orphan designation. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that the proposed product might be of potential significant benefit for the treatment of chronic iron overload, particularly in terms of its pharmacological mode of action and oral mode of

^{*}Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.

administration resulting in significant contribution to patient care. The assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?

The proposed product is an iron chelator. Iron chelators are molecules binding to iron in the body, allowing it to then be eliminated through urinary or intestinal routes at a higher rate than the natural very low iron elimination rate (through shedding of skin and mucosal cells, menstruation or other blood loss).

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials in patients with chronic iron overload requiring chelation therapy were ongoing.

The medicinal product was not marketed anywhere worldwide for chronic iron overload requiring chelation therapy, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 6 November 2003 a positive opinion recommending the grant of the above-mentioned designation.

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 Community) 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:

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Translations of the active ingredient and indication in all EU languages

Language	Active Ingredient	Indication
English	4,5-dihydro-2-(2,4-dihydroxyphenyl)-4-	Treatment of chronic iron overload
	methylthiazole-4(S)-carboxylic acid	requiring chelation therapy
Danish	4,5-dihydro-2-(2,4-dihydroxyfenyl)-4-	Behandling af kronisk jern overskud,
	metylthiazol-4(S)-karboxylsyre	der nødvendiggør chelat behandling
Dutch	4,5-dihydro-2-(2,4-dihydroxyfenyl)-4-	Behandeling van chronische
	methylthiazol-4(S)-carbonzuur	ijzerstapeling welke chelatie
		therapie vergt
Finnish	4,5-dihydro-2-(2,4-dihydroksifenyyli)-4-	Kroonisen, kelatointihoitoa vaativan
	metyylitiatsoli-4(S)-karboksyylihappo	raudan liikavarastoitumisen hoito
French	Acide carboxylique 2- 4,5-dihydro-2-(2,4-	Traitement de la surcharge ferrique
	dihydroxyphényl)-4-méthylthiazole-4(S)	chronique nécessitant un traitement
		chélateur
German	4,5-Dihydro-2-(2,4-dihydroxyphenyl)-4-	Behandlung der Eisenüberladung
	methylthiazol-4(S)-Carbonsäure	welche Chelattherapie benötigt
Greek	4,5-διύδρο-2-(2,4-διυδρόξυφαινυλο)-4-	θεραπεία της χρόνιας υπερφόρτωσης
	μεθυλδιαζόλη-4(S)-καρβοξυλικό οξύ	σιδήρου με χηλικούς παράγοντες
Italian	Acido 4,5-didro-2-(2,4-didrossifenil)-4-	Trattamento dell'accumulo cronico
	metiltiazolo -4(S)-carbossilico	di ferro che necessita di terapia
		chelante
Portuguese	Ácido 4,5-dihidro-2-(2,4-dihidroxifenil)-	Tratamento da sobrecarga crónica de
	4-metiltiazol-4(S) carboxílico	ferro que necessita uma terapia
		quelante
Spanish	Ácido 4,5-dihidro-2-(2,4-dihidroxifenil)-	Tratamiento de la sobrecarga crónica
	4-metiltiazol-4(S)-carboxílico	de hierro que necesita de terapia
		quelante.
Swedish	4,5-dihydro-2-(2,4-dihydroxifenyl)-4-	Behandling av kronisk
	metyltiazol-4(S)-karbonsyra	järnupplagring som kräver
		kelatterapi