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Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of

l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane for treatment to mobilize progenitor cells prior to stem cell transplantation

On 20 October 2004, orphan designation (EU/3/04/227) was granted by the European Commission to Orphix Consulting GmbH, Germany, for l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11-tetraazacyclotetradecane for treatment to mobilize progenitor cells prior to stem cell transplantation. The sponsorship was transferred to Genzyme Europe BV, The Netherlands, in June 2007.

What is stem cell transplantation?

The term "progenitor cell" or "stem cell" is used to indicate those cells which are still immature and do not express all the characteristics of the future mature cells which will derive from them. Haematopoietic progenitor cells are able to produce the cells of the immune system and bone marrow. For diseases where the bone marrow or the immune system are absent, or working abnormally, or invaded by cancer cells, it is sometimes appropriate to use a treatment called haematopoietic progenitor cell transplantation. This consists of replacing the abnormal cells of the immune system and bone marrow, and introducing new progenitor cells. Two types of stem cell transplants can be used: autologous blood stem cell transplants using the patient's own blood stem cells, or allogeneic blood stem cell transplants using the blood stem cells from another person ("donor"). Diseases requiring such transplantation are life-threatening.

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

At the time of designation, treatment to mobilize progenitor cells prior to stem cell transplantation affected less than 1 in 10,000 people in the European Union (EU)*. This is equivalent to a total of fewer than 46,000 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?

Mobilisation therapies aim at bringing the progenitor cells into peripheral blood to improve the yield of cells which can be collected for subsequent transplantation. Several medicines can be used in order to mobilise the stem cells such as chemotherapy (using drugs to destroy cells) or haematopoietic growth factors (drugs that stimulate the proliferation of the blood cells).

l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane might be of potential significant benefit for the mobilisation therapy. This 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?

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004).

l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane might stimulate the mobilization of the stem cells into peripheral blood by inhibiting a substance called chemokine that normally prevents the progenitor cells from migrating out of the bone marrow.

What is the stage of development of this medicine?

The effects of l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients undergoing stem cell transplantation were ongoing.

The medicinal product was not marketed anywhere worldwide for treatment to mobilize progenitor cells prior to stem cell transplantation, at the time of submission. Orphan designation of l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane was granted in the United States for the indication “to improve the yield of progenitor cells in the apheresis product for subsequent stem cells transplantation following myelosuppressive or myeloablative chemotherapy”.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 9 September 2004 a positive opinion recommending the grant of the above-mentioned designation.

Update: l, l'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane (Mozobil) has been authorised in the EU since 31 July 2009. Mozobil is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.

For more information on <Tradename>, see:

www.emea.europa.eu/humandocs/Humans/EPAR/mozobil/mozobil.htm

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
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	1, 1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane	Treatment to mobilize progenitor cells prior to stem cell transplantation
Czech	1, 1'-[1,4-fenylenbis(methylen)]-bis-1,4,8,11-tetraazacyklotetradekan	Stimulace mobilizace periferních kmenových buněk určených k transplantaci
Danish	1, 1'-[1,4-phenylenebis(methylen)]-bis-1,4,8,11-tetraazacyclotetradecan	Behandling til forudgående mobilisering af progenitorceller til stamcelletransplantation
Dutch	1, 1'-[1,4-fenyleenbis(methyleen)]-bis-1,4,8,11-tetra-azacyclotetradecaan	Behandeling tot mobilisatie van progenitorcellen voorafgaand aan stamceltransplantatie
Estonian	1, 1'-[1,4-fenüleenbis(metüleen)]-bis-1,4,8,11-tetraasatsüklotetradekaani	Ravi vereloome eellasrakkude mobiliseerimiseks enne tüvirakkude siirdamist
Finnish	1, 1'-[1,4-fenyleenibis(metyleen)]-bis-1,4,8,11-tetra-atsasyklotetradekaani	Eisolujen mobilisointiin ennen kantasolusiirtoa
French	1, 1'-(1,4-phénylènebisméthylène)-bis-1,4,8,11-tétraazacyclotétradecane	Traitement pour la mobilisation des cellules progénitrices avant greffe de cellules souches
German	1, 1'-[1,4-phenylen-bis(methylen)]bis-1,4,8,11-tetraazazyklotetradekan	Behandlung zur Mobilisierung von Vorläuferzellen vor Stammzelltransplantation
Greek	1, 1'-[1,4-φαινυλένο- δις (μεθυλένιο)]-δις-1,4,8,11-τετρα-αζα-κυκλο-τετραδεκάνιο	Θεραπεία για την κινητοποίηση προγονικών κυττάρων που προηγείται της μεταμόσχευσης βλαστικών κυττάρων
Hungarian	1, 1'-[1,4-fenilén-bisz(metilén)]-bis-1,4,8,11-tetraazaciklotetradekán	Őssejt transzplantációt megelőző progenitor sejt mobilizáló kezelés
Italian	1, 1'-[1,4-fenilene bis(metilene)]-bis-1,4,8,11-tetraazaciclotetradecano	Trattamento per la mobilizzazione delle cellule progenitrici precedente per il trapianto di cellule staminali
Latvian	1, 1'-[1,4-fenilēn-bis(metilēn)]-bis-1,4,8,11-tetraazaciklotetradekāns	Ārstēšana priekšteču šūnu mobilizēšanai pirms cilmes šūnu transplantācijas
Lithuanian	1, 1'-[1,4-fenilenebis(metilenas)]-bis-1,4,8,11-tetraazaciklotetradekanas	Gydymas, siekiant mobilizuoti ląsteles – pirmtakus prieš kamieninių ląstelių transplantaciją
Maltese	1, 1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane	Treatment to mobilize progenitor cells prior to stem cell transplantation

Polish	1, 1'-[1,4-fenilenobis(metyleno)]-bis-1,4,8,11-tetraazacyklotetradekanonian	Leczenie w celu wcześniejszej mobilizacji komórek prekursorowych przed transplantacją komórek macierzystych
Portuguese	1, 1'-[1,4-fenilenobis (metileno)]-bis-1,4,8,11-tetraazaciclotetradecano	Tratamento prévio ao transplante de células indiferenciadas para mobilizar células progenitoras
Slovak	1,1'-[1,4-fenylénbis(metylén)]-bis-1,4,8,11-tetraazacyklotetradekán	Liečba na mobilizáciu progenitorových buniek pred transplantáciou kmeňových buniek
Slovenian	1, 1'-[1,4-fenilenbis (metilen)]-bis-1,4,8,11-tetraazacyklotetradekan	Mobilizacija prekurzorskih celic pred transplantacijo krvotvornih matičnih celic
Spanish	1, 1'-[1,4-fenilenbis (metilén)]-bis-1,4,8,11-tetraazaciclotetradecano	Tratamiento para la movilización de células progenitoras con anterioridad al trasplante de células madre
Swedish	1,1'-[1,4-fenilen-bis(metylen)]-bis-1,4,8,11-tetraazacyklotetradekan	Behandling för att mobilisera progenitorceller inför stamcellstransplantation
Norwegian	1, 1'-[1,4-fenilenbis(metylen)]-bis-1,4,8,11-tetraazacyklotetradekan	Behandling for mobilisering av progenitorceller før stamcelletransplantasjon.
Icelandic	1, 1'-[1,4-fenýlenebis (metýlen)]-bis-1,4,8,11-tetraazacyklótetradekan	Formeðferð fyrir stofnfrumuígræðslu til að koma hreyfingu á stofnfrumur