11 November 2010
EMA/COMP/577300/2010 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(manganese, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-) for the prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

On 31 January 2008, orphan designation (EU/3/07/522) was granted by the European Commission to Celtic Bio-Pharma Services Ltd, United Kingdom, for (manganese, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-), for the prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy.

What is oral mucositis?

Radiation therapy is often used as a treatment option in selected tumours. The technique employs high-dose x-rays or other high-energy rays to kill cancer cells. Radiation therapy will not only kill the tumour cells, but will unfortunately also cause some degree of injury (e.g., inflammation) to the surrounding cells and tissues. Radiation therapy applied to tumours located in the head and neck region usually damages the inner lining (mucosa) of the mouth. The damage results in inflammation, ulcers, severe pain, bleeding and dryness of the mouth. This complication of radiation therapy is called "oral mucositis". The condition is chronically debilitating as it causes severe pain and leads to difficulty or inability to swallow, and consequently to malnutrition.

What is the estimated number of patients at risk of developing the condition?

At the time of designation, the number of patients at risk of oral mucositis in head and neck cancer patients undergoing radiation therapy was estimated to be approximately 2.8 people in 10,000 in the European Union (EU)*. This is equivalent to a total of around 140,000 people, which is below the

*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 27), Norway, Iceland and Lichtenstein. This represents a population of 498,000,000 (Eurostat 2006). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2010. Reproduction is authorised provided the source is acknowledged.

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 methods of prevention are available?

No satisfactory methods exist that were authorised at the time of application.

How is this medicine expected to work?

The medicinal product mimics the action of a natural component of the cells, an enzyme called superoxide dismutase. Superoxide dismutase is thought to have a double effect, firstly it can reduce inflammation, and secondarily it can decrease the rate of programmed cell death (apoptosis). As mucositis involves inflammation, the positive effect of the product over this process, as well as the reduced rate of apoptosis, is expected to have a beneficial effect in the condition.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of (manganese, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-) in experimental models was ongoing; clinical trials in head and neck cancer patients receiving radiotherapy had not started yet.

The medicinal product was not marketed anywhere worldwide as a medicinal product for prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 6 December 2007 recommending the granting of this 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 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:

Celtic Bio-Pharma Services Ltd
Sheridan House, St Ann's Road
Harrow, Middlesex HA1 1JU
United Kingdom
Telephone: +44 208 997 2988
Telefax: +44 208 997 2988
E-Mail: gmcgettigan@celticbio.net

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	(manganese, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21°-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-)	Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy
Bulgarian	(манганов, дихлоро [(4aR, 13aR, 17aR, 21aR)- 1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21º-еикозахидро-11, 7-нитрило-7H-дибензо[b,h] [1,4,7,10] тетраазациклохептадецин-κN5, κN13, κN18, κN21, κN22]-)	Профилактика на орален мукозит при пациенти с карцином в областта на главата и шията, подложени на радиационна терапия
Czech	(dichlor manganu [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-)	Prevence orální mukositidy u pacientů s nádorovým onemocněním v oblasti hlavy a krku podstupujících radioterapii
Danish	(mangan, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Forebyggelse af *oral mucositis* i patienter med kræft i hoved- og halsregionen som får strålebehandling
Dutch	(mangaan, di-chloor [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetra-azacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-)	Preventie van orale mucositis in hoofd- en nekkankerpatienten die stralingstherapie ondergaan
Estonian	(mangaan, dikloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikosahüdro-11, 7-nitrilo-7H-dibenso[b,h] [1,4,7,10] tetraasatsüklolоheptadetsiin-κN5, κN13, κN18, κN21, κN22]-)	Suuõõne mukosiidi profülaktika patsientidel, kes saavad kiiritusravi pea- ja kaelapiirkonna vähi vastu

[1] At the time of designation

Language	Active Ingredient	Indication
Finnish	(manganeesi, dikloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikosahydro-11, 7-nitrilo-7H-dibentsooli[b,h] [1,4,7,10] tetra-atsasykloheptadekiini-κN5, κN13, κN18, κN21, κN22]-)	*Oraalisen mucositis*:in ennaltaehkäisy pään- ja kaulan alueen syöpää sairastavilla potilailla, jotka saavat sädehoitoa
French	(manganèse, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tétraazacycloheptadécine-κN5, κN13, κN18, κN21, κN22]-)	Prévention de la mucite bucco-pharyngée chez les patients atteints de cancer de la tête et du cou subissant une radiothérapie
German	(Mangandichlor [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-Nitril-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Prävention der *oralen Mucositis* (Schleimhautentzündung im Mund) nach Radiotherapie im Kopf- und Halsbereich gegen Krebs
Greek	(μαγγάνιο, διχλωρο [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-εικοσαϋδρο-11, 7-νιτρίλο-7^{H}-διβενζο [b,h] [1,4,7,10] τετραζακυκλοεπταδεκίνη-κN5, κN13, κN18, κN21, κN22]-)	Πρόληψη της στοματίτιδας σε ασθενείς με καρκίνο της κεφαλής και του λαιμού που υποβάλλονται σε ακτινοθεραπεία
Hungarian	(mangán, diklór [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahidro-11, 7-nitril-7H-dibenzo[b,h] [1,4,7,10] tetraazaciklohéptadecine-κN5, κN13, κN18, κN21, κN22]-)	Fej- és nyakrák sugárkezelését követő orális mucositis megelőzése
Italian	(manganese, dicloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosaidro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacicloeptadecina-κN5, κN13, κN18, κN21, κN22]-)	Prevenzione delle mucositi orali in pazienti con cancro nella regione della testa e del collo sottoposti a radioterapia
Latvian	(mangāns, dihlor [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21°-eikosahidro-11, 7-nitril-7H-dibenzo[b,h] [1,4,7,10] tetraazaciklohéptadecīns-κN5, κN13, κN18, κN21, κN22]-)	Mutes gļotādas iekaisuma novēršana galvas un kakla vēža pacientiem, kas saņem staru terapiju

Language	Active Ingredient	Indication
Lithuanian	(mangano, dichlor[(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikozahidro-11, 7-nitril-7H-dibenzo[b,h] [1,4,7,10] tetraazacikloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Burnos gleivinės uždegimo (mukozito) prevencija pacientams, kuriems taikomas radioterapinis gydymas dėl galvos ir kaklo srities vėžio
Maltese	(manganese, dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21°-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacycloheptadecine-κN5, κN13, κN18, κN21, κN22]-)	Prevenzjoni tal-mukożite orali f'pazjenti li għandhom kanċer fir-ras u fl-għonq li qed jirċievu radjoterapija
Polish	Dichloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikozanohydro-11, 7-nitrilo, 7H-dibenzo[b,h], [1,4,7,10] tetraazacykloheptadecynian-κN5, κN13, κN18, κN21, κN22]-manganu	Zapobieganie zapaleniu śluzówki jamy ustnej u pacjentów poddawanych radioterapii w przebiegu raka głowy i szyi
Portuguese	(manganês, dicloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahidro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacicloheptadecina-κN5, κN13, κN18, κN21, κN22]-)	Prevenção da mucosite oral induzida pela radioterapia em doentes com neoplasia de cabeça e pescoço.
Romanian	(Mangan, dicloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahidro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacicloheptadecină-κN5, κN13, κN18, κN21, κN22]-)	Prevenirea mucozitei orale la pacienţii cu neoplasm de cap şi gât cărora li se administrează radioterapie
Slovak	(mangán, dichlór [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikozahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacykloheptadecín-κN5, κN13, κN18, κN21, κN22]-)	Prevencia orálnej mukozitídy u pacientov podstupujúcich rádioterapiu pri liečbe rakoviny hlavy a krku
Slovenian	(mangan, dikloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikozahidro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazacikloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Preprečevanje oralnega mukozitisa pri pacientih, ki so izpostavljeni radioterapiji v območju glave in vratu
Spanish	(manganeso, dicloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahidro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetra-aza-cicloheptadecina-κN5, κN13, κN18, κN21, κN22]-)	Prevención de la mucositis oral en pacientes tratados con radioterapia por cánceres de la región de la cabeza y el cuello

Language	Active Ingredient	Indication
Swedish	(mangan, dikloro [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eikosahydro-11, 7-nitrilo-7H-dibenso[b,h] [1,4,7,10] tetraazacykloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Profylax av *oral mucositis* hos huvud-hals cancer patienter som får strålbehandling
Norwegian	(mangan, diklor [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicosahydro-11, 7-nitrilo-7H-dibenzo[b,h] [1,4,7,10] tetraazasykloheptadecin-κN5, κN13, κN18, κN21, κN22]-)	Forebygging av *oral mucositis* hos pasienter med kreft i hode- og halsregionen som får strålebehandling
Icelandic	(mangan, díchlóró [(4aR, 13aR, 17aR, 21aR)-1, 2, 3, 4, 4a, 5, 6, 12, 13, 13a, 14, 15, 16, 17, 17a, 18, 19, 20, 21, 21a-eicósahýdró-11, 7-nitríló-7H-díbenzó[b,h] [1,4,7,10] tetraazacýclóheptadecín-κN5, κN13, κN18, κN21, κN22]-)	Vörn gegn slímubólgu í munni hjá sjúklingum í geislamedferð vegna krabbameins á höfuð-og hálssvæði