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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A for the treatment of myasthenia gravis

On 21 May 2015, orphan designation (EU/3/15/1489) was granted by the European Commission to Toleranzia AB, Sweden, for fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A for the treatment of myasthenia gravis.

What is myasthenia gravis?

Myasthenia gravis is a disease that leads to muscle weakness and tiredness. It is an autoimmune disorder in which the immune system (the body's natural defences) attacks and damages 'acetylcholine receptors' on the surface of muscle cells. For a muscle to contract, a substance called acetylcholine is released from a nerve and attaches to the acetylcholine receptors on the muscle cells. In myasthenia gravis, because of the damage to these receptors, the muscles are not able to contract as well as normal. In most patients, the disease is associated with abnormalities of a gland in the chest called the thymus, which is part of the immune system.

In myasthenia gravis, the muscles involved in swallowing and those around the eyes are commonly affected first, causing difficulty in swallowing and the eyelids to drop. Muscle weakness typically worsens towards the end of the day and after exercise.

Myasthenia gravis is a long-term debilitating disease and may be life-threatening when the muscles involved in breathing are affected.

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

At the time of designation, myasthenia gravis affected approximately 2 in 10,000 people in the European Union (EU). This was equivalent to a total of around 103,000 people*, and is below the

*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 28), Norway, Iceland and Liechtenstein. This represents a population of 512,900,000 (Eurostat 2015).

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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 designation, a number of medicines were authorised in the EU for the treatment of myasthenia gravis. Surgery to remove the thymus gland (thymectomy) was performed in some patients.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with myasthenia gravis because experimental studies show that it can help improve muscle function. In addition, it acts in a different way to existing treatments and might be able to be used in combination with them. These assumptions will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

The medicine is made up of three protein fragments linked together. One of these fragments is a part of the acetylcholine receptor and it works by inducing immune system tolerance to the acetylcholine receptors. When given to the patient, the medicine is expected to help prevent the immune system from attacking acetylcholine receptors, thereby reducing damage to acetylcholine receptors and helping to control the disease.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with myasthenia gravis had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for myasthenia gravis or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 16 April 2015 recommending the granting of this designation.

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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:

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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	Fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A	Treatment of myasthenia gravis
Bulgarian	Фузионни протеини, съставени от генно модифицирана субединица A1 на холерен токсин, пептиди от алфа веригата на ацетилхолиновия рецептор и димер на D-фрагмента от протеин A на *Staphylococcus aureus*	Лечение на миастения гравис
Croatian	Fuzijski proteini koji se sastoje od genetički modificirane podjedinice A1 toksina kolere, peptida iz alfa lanca acetilkolinskog receptora i dimera D fragmenta proteina A iz *Staphylococcus aureus*	Liječenje miastenije gravis
Czech	Fúzní proteiny skládající se z geneticky modifikovaného cholerového toxinu podjednotka A1, peptidů alfa řetězce acetylcholinového receptoru a dimeru domény D z proteinu A *Staphylococcus aureus*	Léčba myasthenie gravis
Danish	Fusionsproteiner sammensat af et genetisk modificeret kolera toksin underenhed A1, peptider fra acetylcholinreceptor alfa-kæden og en dimer af D-fragmentet fra *Staphylococcus aureus* protein A	Behandling af myasthenia gravis
Dutch	Fusie-eiwitten bestaande uit een genetisch gemodificeerde choleratoxine ondereenheid A1, peptiden van de acetylcholinereceptor alfaketen en een dimeer van het D-fragment van *Staphylococcus aureus* proteïne A	Behandeling van myasthenia gravis
Estonian	Fusioonvalgud, mis koosnevad geneetiliselt muundatud kooleratoksiini allüksusest A1, atsetüülkoliini retseptori alfa-ahela peptiididest ja *Staphylococcus aureus*'e A-valgu D-fragmendi dimeerist	Myasthenia Gravise ravi
Finnish	Fuusioproteiinit, jotka koostuvat koleratoksiinin geneettisesti modifioidusta alayksiköstä A1, asetyylikoliinireseptorin alfaketjusta johdetuista peptideistä ja *Staphylococcus* aureuksen proteiini A:n D-fragmentin dimeeristä	Myasthenia graviksen hoito
French	Protéines de fusion composées de la Toxine sous-unité A1 de choléra génétiquement modifiée, de peptides de la chaîne alpha du récepteur de l'acétylcholine et d'un dimère du fragment D de la protéine A du staphylocoque doré	Traitement de la myasthénie grave

[1] At the time of designation

Language	Active ingredient	Indication
German	Fusionsproteine bestehend aus einem gentechnisch veränderten Choleratoxin Subeinheit A1, Peptide aus der Alpha-Kette des Acetylcholinrezeptors und einem Dimer des D-Fragments des *Staphylococcus aureus* Protein A	Behandlung der Myasthenia Gravis
Greek	Πρωτεΐνες σύντηξης αποτελούμενες από γενετικά τροποποιημένη υπομονάδα Α1 της τοξίνης της χολέρας, πεπτίδια της α-αλυσίδας του υποδοχέα της ακετυλοχολίνης και ένα διμερές του τμήματος D της πρωτεΐνης Α του χρυσίζοντος σταφυλόκοκκου	Θεραπεία της βαρείας μυασθένειας
Hungarian	Genetikailag módosított kolera toxin A1 alegységből,, az acetilkolin-receptor alfa láncából származó peptidekből és a *Staphylococcus aureus* fehérje A D fragmentumának egy dimerjéből álló fúziós proteinek	Myasthenia gravis kezelése
Italian	Proteine di fusione composte da una subunità sottounità A1 geneticamente modificata della tossina colerica, da peptidi della catena alfa del recettore dell'acetilcolina e da un dimero del frammento D della proteina A di *Staphylococcus aureus*	Trattamento della miastenia grave
Latvian	Sapludināti proteīni, kas sastāv no ģenētiski modificēta holēras toksīna apakšvienības A1, peptīdiem no acetilholīna receptora alfa ķēdes un D fragmenta dimēra no *Staphylococcus aureus* proteīna A	Myasthenia gravis ārstēšanai
Lithuanian	Baltymų, sudarytų iš genetiškai modifikuoto choleros toksino subvieneto A1, alfa grandinės acetilcholino receptoriaus peptidų ir *Staphylococcus aureus* A baltymo D fragmento dimero, lydinys	Generalizuotos miastenijos gydymas
Maltese	Proteini ta' fużjoni magħmula mill-parti A1 tat-tossin tal-kolera modifikata ġenitikament, peptidi mill-katina alfa tar-riċettur ta' *acetylcholine* u dimer tal-framment D mill-proteina A ta' *Staphylococcus aureus*	Kura ta' myasthenia gravis
Polish	Białka fuzyjne składające się z modyfikowanej genetycznie podjednostki A1 toksyny przecinkowca cholery, peptydów łańcucha alfa receptora acetylocholinowego i dimeru fragmentu D białka A gronkowca złocistego Public summary of opinion on orphan designation (*Staphylococcus aureus*)	Leczenie miastenii gravis
Portuguese	Proteínas de fusão compostas por uma subunidade A1 da Toxina do Cólera, geneticamente modificada, péptidos da cadeia alfa do recetor da acetilcolina e um dímero do fragmento D da proteína A de *Staphylococcus aureus*	Tratamento da miastenia gravis
Romanian	Proteine de fuziune compuse din subunitatea A1 modificată genetic a toxinei holerice , peptide din lanțul alfa al receptorului pentru acetilcolină și un dimer al fragmentului D al proteinei A a *Staphylococus aureus*	Tratamentul miasteniei gravis

Language	Active ingredient	Indication
Slovak	Fúzné proteíny skladajúce sa z geneticky modifikovaného cholerového toxinu podjednotka A1, peptidov alfa raťzca z acetylcholinového receptora a diméru domény D z proteínu A *Staphylococcus aureus*	Liečba myasthenie gravis
Slovenian	Fuzijski proteini, sestavljeni iz gensko spremenjenega toksina kolere podenoti A1, peptidov iz verige alfa acetilholinskega receptorja in dimerja fragmenta D iz proteina A *Staphylococcus* aureusa	Zdravljenje miastenije gravis
Spanish	Proteínas de fusión compuestas por un fragmento subunidad A1 de la toxina colérica genéticamente modificado, péptidos de la cadena alfa del receptor de la acetilcolina y un dímero del fragmento D de la proteína A de *Staphylococcus aureus*	Tratamiento de la miastenia gravis
Swedish	Fusionsproteiner bestående av genetiskt modifierat koleratoxin underenhet A1, peptider från acetylkolinreceptor-alfakedjan och en dimer från D-fragmentet från *Staphylococcus aureus* protein A	Behandling av myasthenia gravis
Norwegian	Fusjonsproteiner bestående av en genetisk modifisert koleratoksin subenhet A1, peptider fra acetylkolinreseptor-alfakjeden og en dimer av D-fragmentet fra *Staphylococcus aureus* protein A	Behandling av myasthenia gravis
Icelandic	Samrunaprótein gerð úr erfðabreyttu undireiningu A1-kólerueitri, peptíðum úr keðju alfakólínviðtaka og tvíliðu D-brots úr A-próteini *Staphylococcus aureus*	Meðferð við vöðvaslensfári