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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium;2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate for the treatment of familial amyloid polyneuropathy

First publication	1 April 2009
Rev.1: transfer of sponsorship	12 November 2009
Rev.2: transfer of sponsorship	18 February 2013
Rev.3: information about Marketing Authorisation	25 July 2013

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 28 August 2006, orphan designation (EU/3/06/401) was granted by the European Commission to ICON Clinical Research Limited, United Kingdom for N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate for the treatment of familial amyloid polyneuropathy.

The sponsorship was transferred to FoldRx Pharmaceuticals Limited, United Kingdom, in September 2009 and to Pfizer Limited, United Kingdom, in May 2012.

What is familial amyloid polyneuropathy?

Familial amyloid polyneuropathy is a hereditary (familial) disease caused by one defective gene which regulates the production of a protein called transthyretin, which is involved in the transport of various substances in the blood. Transthyretin is primarily produced in the liver. The normal form of transthyretin is a homotetramer (it is made up of four identical parts attached to each other). In affected patients, the protein is modified in a way that makes it break up and lose its function. The broken up parts of the initial protein then start accumulating and depositing in, so called, amyloid structures, in various tissues (including the nervous system) and eventually interfere with organ function. The primary symptom of the condition is progressive loss of neurological functions (polyneuropathy). Additionally, the eyes and kidneys can become affected. Familial amyloid polyneuropathy is chronically debilitating and life-threatening.

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

At the time of designation familial amyloid neuropathy affected less than 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 4,600 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?

The only available treatment of the condition is liver transplantation; surgically removing the liver and replacing it with a liver from a donor that produces the healthy unmodified transthyretin. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate might be of potential significant benefit for the treatment of familial amyloid polyneuropathy, mainly because it has a new mechanism of action and may be used in patients for whom liver transplantation is unavailable. 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?

N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate is a molecule designed to bind to and stabilise the transthyretin homotetramer. According to the sponsor, it will thus prevent the protein from breaking up and decrease the amount of harmful amyloid deposits in the organs of the affected patients.

What is the stage of development of this medicine?

The effects of N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate were evaluated in experimental models. At the time of submission of the application for orphan designation, clinical trials in patients with familial amyloid polyneuropathy were ongoing.

N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate was not authorised anywhere worldwide for the treatment of familial amyloid polyneuropathy nor 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 12 July 2006 recommending the granting of this designation.

Update: N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl) ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate (Vyndaqel) has been authorised in the EU since 16 November 2011 for the treatment of transthyretin amyloidosis in adult patients with stage-1 symptomatic polyneuropathy to delay peripheral neurologic impairment

*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 25), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 464,200,000 (Eurostat 2004).

More information on Vyndaqel 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

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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	N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate	Treatment of familial amyloid polyneuropathy
Bulgarian	N-метил D-(2,3,4,5,6-пентахидрокси-хексил)-амониев; 2-(3,5-дихлоро-фенил)-бензоксазол-6-карбоксилат	Лечение на фамилна амилоидна полиневропатия
Czech	N-methyl-D-(2,3,4,5,6-pentahydroxyhexyl)-amonium; 2-(3,5-dichlorofenyl)-benzoxazol-6-karboxylát	Léčba familiární amyloidózní polyneuropatie
Danish	N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-diklorfenyl)-benzoxazol-6-karboksylat	Behandling af familiær amyloid polyneuropati
Dutch	N-methyl-D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloor-fenyl)-benzoxazool-6-carboxylaat	Behandeling van familiale amyloïde polyneuropathie
Estonian	N-metüül-D-(2,3,4,5-pentahüdroksüheksüül)-ammoonium; 2-(3,5-diklorofenüül)-bensoksasool-6-karboksülaat	Perekondliku amüloidse polüneuropaatia ravi
Finnish	N-metyyli-D-(2,3,4,5,6-pentahydroksiheksyyli)-ammonium; 2-(3,5-diklorofenyyli)-bentsoksatsoli-6-karboksylaatti	Suvuittain esiintyvän amyloidipolyneuropatian hoito
French	N-méthyle D-(2,3,4,5,6-pentahydroxy-hexyle)-ammonium; 2-(3,5-dichloro-phényle)-benzoxazole-6-carboxylate	Traitement de la neuropathie amyloïde familiale
German	N-Methyl D-(2,3,4,5,6-Pentahydroxyhexyl)-Ammonium; 2-(3,5-Dichlorphenyl)-Benzoxazol-6-Carboxylat	Behandlung der familiären Amyloid-Polyneuropathie
Greek	N-μεθυλο D-(2,3,4,5,6-πενταϋδροξυ-εξυλο)-αμμώνιο. 2-(3,5-διχλωρο-φαινυλο)-6-καρβοξυλική βενζοξαζόλη	Θεραπεία της οικογενούς αμυλοειδικής πολυνευροπάθειας
Hungarian	N-metil-D-(2,3,4,5,6-pentahidroxi-hexil)-ammónium; 2-(3,5-dikloro-fenil)-benzoxazol-6-karboxilát	Familiáris amyloid polyneuropathia kezelése
Italian	N-metil D-(2,3,4,5,6-pentaidrossi-esil)-ammonio; 2-(3,5-dicloro-fenil)-benzossazolo-6-carbossilato	Trattamento della polineuropatia amiloide familiare
Latvian	N-metil-D-(2,3,4,5,6-pentahidroksiheksil)-amonijs; 2-(3,5-dihlorfenil)-benzoksazol-6-karboksilāts	Ģimenes amiloīdas polineiropātijas ārstēšana

[1] At the time of transfer of sponsorship

Language	Active ingredient	Indication
Lithuanian	N-metil D-(2,3,4,5,6-pentahidroksiheksil)-amonis; 2-(3,5-dichlorfenil)-benzoksiazolo-6-karboksilatas	Paveldimos amiloidinės polineuropatijos gydymas
Maltese	N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate	Kura tal-polinewropatija amilojde li tintiret
Polish	N-metylo D-(2,3,4,5,6-pentahydroksy-heksylo)-amon; 2-(3,5-dichloro-fenylo)-benzoksazolo-6-karboksylan	Leczenie polineuropatii w przebiegu amyloidozy rodzinnej
Portuguese	Amónio de N-metil D-(2,3,4,5,6-pentahidroxi-hexil); 2-(3,5-dicloro-fenil)-benzoxazole-6-carboxilato	Tratamento de polineuropatia amilóide familiar
Romanian	N-metil D-(2,3,4,5,6-pentahidroxi-hexil)-amoniu; 2-(3,5-dicloro-fenil)-benzoxazol-6-carboxilat	Tratamentul polineuropatiei amiloide familiale
Slovak	N-metyl-D-(2,3,4,5,6-pentahydroxyhexyl)-amónium; 2-(3,5-dichlorofenyl)-benzoxazol-6-karboxylát	Liečba familiárnej amyloidovej polyneuropatie
Slovenian	N-metil D-(2,3,4,5,6-pentahidroksi-heksil)-amonij; 2-(3,5-dikloro-fenil)-benzoksazol-6-karboksilat	Zdravljenje dedne amiloidne polinevropatije
Spanish	N-metil D-(2,3,4,5,6-pentahidroxi-hexil)-amoniaco; 2-(3,5-dicloro-fenilo)-benzoxazol-6-carboxilato	Tratamiento de polineuropatía amiloide familiar
Swedish	N-metyl D-(2,3,4,5,6-pentahydroxi-hexyl)-ammonium; 2-(3,5-dikloro-fenyl)-benzoxazol-6-karboxylat	Behandling av familjär amyloid polyneuropati
Norwegian	N-metyl D-(2,3,4,5,6-pentahydroksyheksyl)-ammonium; 2-(3,5-diklorfenyl)-benzoxazol-6-karboksylat	Behandling av familiær amyloid polyneuropati
Icelandic	N-metýl D-(2,3,4,5,6-pentahýdroxý-hexýl)-ammóníum; 2-(3,5-tvíklóró-fenýl)-benzoxazól-6-karboxýlat	Meðferð við ættgengum mýlildisfjöltaugakvilla