



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/COMP/697127/2013
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride for the treatment of progressive familial intrahepatic cholestasis

On 16 January 2014, orphan designation (EU/3/13/1216) was granted by the European Commission to Lumena Pharma UK Limited, United Kingdom, for (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride for the treatment of progressive familial intrahepatic cholestasis.

What is progressive familial intrahepatic cholestasis?

Progressive familial intrahepatic cholestasis is an inherited condition that causes progressive liver disease, which normally leads to liver failure. In progressive familial intrahepatic cholestasis, bile acids, essential components of bile (a fluid produced by the liver which helps digestion), build up in liver cells, becoming toxic to the liver and causing cirrhosis (scarring). Symptoms usually begin in infancy and include severe itching, jaundice (yellowing of the skin and eyes), delayed growth, pancreatitis (inflammation of the pancreas) and bleeding inside the stomach or the gut. At later stages, high blood pressure in the vein that supplies blood to the liver and liver failure will appear.

Progressive familial intrahepatic cholestasis is a long-term debilitating and life-threatening condition because, when the disease progresses, it may lead to liver cirrhosis and liver failure, and may increase the risk of liver cancer.

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

At the time of designation, progressive familial intrahepatic cholestasis affected not more than 0.2 in 10,000 people in the European Union (EU). This was equivalent to a total of not more than 10,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on

* 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 512,200,000 (Eurostat 2013).



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 orphan designation, no satisfactory treatments were authorised in the EU for progressive familial intrahepatic cholestasis. Several medicines were used to treat the itching. Patient with end-stage liver disease would undergo liver transplantation.

How is this medicine expected to work?

The medicine is expected to reduce the amount of bile acid in the liver. It is expected to do so by interfering with the process by which most bile acids in the intestines are recovered and delivered back to the liver through the blood.

This medicine is thought to act locally on the intestines, blocking certain channels called ileal bile acid transporters through which the bile acids leave the intestine to reach the blood vessels that carry them back to the liver. By blocking these channels, the medicine is expected to help reduce the amount of bile acids in the liver, thereby reducing the liver damage and itching seen in patients with progressive familial intrahepatic cholestasis.

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 the medicinal product in experimental models was ongoing.

At the time of submission, no clinical trials with the medicine in patients with progressive familial intrahepatic cholestasis had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for progressive familial intrahepatic cholestasis 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 6 November 2013 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:

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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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl)methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride	Treatment of progressive familial intrahepatic cholestasis
Bulgarian	(4R,5R)-1-[[4-[[4-[3,3-дибутил-7-(диметиламино)-2,3,4,5-тетрахидро-4-хидрокси-1,1-диоксидо-1-бензотиепин-5-ил]фенокси)метил]фенил]метил]-4-аза-1-азониабцикло[2.2.2]октан хлорид	Лечение на прогресивна фамилна интрахепатална холестаза
Czech	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]fenoksi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2] oktan-chlorid	Léčba progresivní familiární intrahepatální cholestázy
Croatian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]fenoksi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]oktanolid	Liječenje progresivne obiteljske intrahepatične kolestaze
Danish	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]fenoxy)metyl]fenyl]metyl]-4-aza-1-azoniabicyclo[2.2.2]oktan klorid	Behandling af progressiv familiær intrahepatisk kolestase
Dutch	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepine-5-yl]fenoxy)methyl]fenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octaan chloride	Behandeling van progressieve familiale intrahepatische cholestase
Estonian	(4R,5R)-1-[[4-[[4-[3,3-dibutüül-7-(dimetüülamino)-2,3,4,5-tetrahüdro-4-hüdroksü-1,1-dioksido-1-bensotiepiin-5-üül]fenoksü]metüül]fenüül]metüül]-4-asa-1-asoniabitüklo[2.2.2]oktaan-kloriid	Progresseeruva perekondliku intrahepaatilise kolestaasi ravi
Finnish	(4R,5R)-1-[[4-[[4-[3,3-dibutyyl-7-(dimetyyliamino)-2,3,4,5-tetrahydro-4-hydroksi-1,1-dioksido-1-bentsotiepiini-5-yyli]fenoksi]metyyli]fenyyli]metyyli]-4-atsa-1-atsoniabisyklo[2.2.2] oktaanikloridi	Etenevän familiaalisen intrahepaattisen kolestaasin hoito
French	Chlorure de (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(diméthylamino)-2,3,4,5-tétrahydro-4-hydroxy-1,1-dioxydo-1-benzothiépine-5-yl]phénoxy]méthyl]phényl] méthyl]-4-aza-1-azoniabicyclo[2.2.2]octane	Traitement de la cholestase intrahépatique familiale progressive

¹ At the time of designation

Language	Active ingredient	Indication
German	(4R,5R)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxid-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octan-chlorid	Behandlung progressiver familiärer intrahepatischer Cholestase
Greek	Χλωριούχο (4R,5R)-1-[[4-[[4-[3,3-διβουτυλ-7-(διμεθυλαμινο)-2,3,4,5-τετραϋδρο-4-υδροξυ-1,1-διοξιδιο-1-βενζοθειεπιν-5-yl]φαινοξυ]μεθυλ]φαινουλ]μεθυλ]-4-αζα-1-αζονιαδικυκλο[2.2.2]οκτάνιο	Θεραπεία της προοδευτικής οικογενούς ενδοηπατικής χολόστασης
Hungarian	(4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetil-amino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dioxid-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2]oktán klorid	Progresszív familiáris intrahepaticus cholestasis kezelése
Italian	(4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilammino)-2,3,4,5-tetraidro-4-idrossi-1,1-diossido-1-benzotiepina-5-il]fenossi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]ottano cloruro	Trattamento della Colestasi progressiva familiare intraepatica
Latvian	(4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroksi-1,1-dioksid-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2]oktāna hlorīds	Progresīvās ģimenes intrahepatiskās holestāzes ārstēšana
Lithuanian	(4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroksi-1,1-dioksido-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2]oktano chloridas	Progresuojančios šeiminės intrahepatinės cholestazės gydymas
Maltese	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride	Kura tal-kolestasi intra-epatika li tintiret progressiva
Polish	Chlorek (4R,5R)-1-[[4-[[4-[3,3-dibutylo-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroksy-1,1-dwutleno-1-benzotiepino-5-yl]fenoksy]metylo]fenylo]metylo]-4-aza-1-azoniobicyklo[2.2.2]oktanu	Leczenie postępującej rodzinnej cholestazy wewnątrzwątrobowej
Portuguese	Cloreto de (4R,5R)-1-[[4-[[4-[3,3-dibutilo-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dióxido-1-benzotiepina-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]octano	Tratamento da colestase intra-hepática familiar progressiva
Romanian	Clorură de (4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dioxido-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]octan	Tratamentul colestazei intrahepatice familiale progresive

Language	Active ingredient	Indication
Slovak	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzotiepin-5-yl]fenoxy]metyl]fenyl]metyl]-4-aza-1-azoniabicyklo[2.2.2]oktán chlorid	Liečba progresívnej familiárnej intrahepatálnej cholestázy
Slovenian	(4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroksi-1,1-dioksido-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2]oktan klorid	Zdravljenje progresivne familiarne intrahepatične holestaze
Spanish	Cloruro de (4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamina)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dióxido-1-benzotiepina-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]octano	Tratamiento de la colestasis intrahepática familiar progresiva
Swedish	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzotiepin-5-yl]fenoxy]metyl]fenyl]metyl]-4-aza-1-azoniabicyklo[2.2.2]oktanklorid	Behandling av progressiv familjär intrahepatisk kolestas
Norwegian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroksey-1,1-dioksido-1-benzotiepin-5-yl]fenoksy]metyl]fenyl]metyl]-4-aza-1-azoniabisyklo[2.2.2]oktanklorid	Behandling av progressiv familiar intrahepatisk kolestase
Icelandic	(4R,5R)-1-[[4-[[4-[3,3-díbútyl-7-(dímetýlamínó)-2,3,4,5-tetrahýdró-4-hýdroxý-1,1-díoxíðó-1-bensótíepín-5-ýl]fenoxy]metýl]fenýl]metýl]-4-asa-1-asóniabisýkló[2.2.2]oktan klórið	Meðferð á ágengri ættgengri innanlifrar gallteppu