



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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 primary sclerosing cholangitis

On 16 January 2014, orphan designation (EU/3/13/1217) 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 primary sclerosing cholangitis.

What is primary sclerosing cholangitis?

Primary sclerosing cholangitis is a disease in which there is long-term inflammation and scarring (fibrosis) of the small bile ducts in the liver. These ducts transport fluid called bile from the liver towards the intestines, where it is used to help digest fats. As a result of the damage to the ducts, bile acids, essential components of bile, build up in the liver and damage the liver tissue. Early symptoms of the disease include tiredness and itching. The disease is more common in middle-aged men.

Primary sclerosing cholangitis is a long-term debilitating and life-threatening disease because, when the disease progresses, it may lead to liver cirrhosis (scarring of the liver) 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, primary sclerosing cholangitis affected not more than 0.3 in 10,000 people in the European Union (EU). This was equivalent to a total of not more than 15,000 people*, and is below the 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).

* 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).



What treatments are available?

At the time of designation, ursodeoxycholic acid was authorised in most EU countries for the treatment of primary sclerosing cholangitis. In advanced cases, the patient may need a liver transplant.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with primary sclerosing cholangitis because experimental studies show its effectiveness in reducing excess bile acids and liver damage. 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 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 itching and liver damage seen in patients with primary sclerosing cholangitis.

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 primary sclerosing cholangitis had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for primary sclerosing cholangitis 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 primary sclerosing cholangitis
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 първичен склерозиращ холангит
Czech	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamino)-2,3,4,5-tetrahydro-4-hidroksi-1,1-dioksido-1-benzotiepin-5-yl]fenoksi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2] oktan-chlorid	Léčba primární sklerotizující cholangitidy
Croatian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamino)-2,3,4,5-tetrahydro-4-hidroksi-1,1-dioksido-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabiciklo[2.2.2]oktanklorid	Liječenje primarnog sklerozirajućeg kolangitisa
Danish	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylamin)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzotiepin-5-yl]fenoxy)metyl]fenyl]metyl]-4-aza-1-azoniabicyclo[2.2.2]oktan klorid	Behandling af primær skleroserende cholangitis
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 primaire scleroserende cholangitis
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-asoniabitšüklo[2.2.2]oktaan-kloriid	Primaarse skleroseeriva kolangiidi 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	Primaarisen sklerosoivan kolangiitin 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 cholangite sclérosante primaire

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 der primär sklerosierenden Cholangitis
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 πρωτοπαθούς σκληρυντικής χολαγγειίτιδας
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	Primer sclerotizáló cholangitis 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 colangite sclerosante primitiva
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	Primārā sklerozējošā holangīta 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	Pirminio sklerozuojančio cholangito 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-kolanġite sklerosanti primarja
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-ylo]fenoksy]metylo]fenylo]metylo]-4-aza-1-azoniobicyklo[2.2.2]oktanu	Leczenie pierwotnego stwardniającego zapalenia dróg żółciowych
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 de colangite esclerosante primária
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 colangitei sclerozante primare

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-benzotiepín-5-yl]fenoxy]metyl]fenyl]metyl]-4-aza-1-azoniabicyklo[2.2.2]oktán chlorid	Liečba primárnej sklerotizujúcej cholangitídy
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 primarnega sklerozirajočega holangitisa
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 colangitis esclerosante primaria
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 primär skleroserande kolangit
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 primær skleroserende cholangitt
Icelandic	(4R,5R)-1-[[4-[[4-[3,3-díbútýl-7-(dímetýlamínó)-2,3,4,5-tetrahýdró-4-hýdroxý-1,1-díoxíðó-1-bensótíepín-5-ýl]fenoxý]metýl]fenýl]metýl]-4-asa-1-asóníabísýkló[2.2.2]oktan klórið	Meðferð við frumkominni herslisgallrásarbólgu