



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

21 January 2014  
EMA/COMP/699781/2013  
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 primary biliary cirrhosis

On 16 January 2014, orphan designation (EU/3/13/1215) 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 primary biliary cirrhosis.

### What is primary biliary cirrhosis?

Primary biliary cirrhosis is a disease in which there is gradual destruction 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 builds up in the liver and damages the liver tissue. Early symptoms of the disease include tiredness and itching. The disease is ten times more common in women than in men.

Primary biliary cirrhosis 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 (inability of the liver to work properly), 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 biliary cirrhosis affected approximately 3 in 10,000 people in the European Union (EU). This was equivalent to a total of approximately 154,000 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).

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\* 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 biliary cirrhosis. 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 biliary cirrhosis because experimental studies show its effectiveness in reducing excess bile acids and damage to the liver. 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 (a major component of bile) 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 acid in the liver, thereby reducing the liver damage and itching seen in patients with primary biliary cirrhosis.

## **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 biliary cirrhosis had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for primary biliary cirrhosis 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.

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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<sup>1</sup>, 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 biliary cirrhosis
Bulgarian	(4R,5R)-1-[[4-[[4-[3,3-дибутил-7-(диметиламино)-2,3,4,5-тетрахидро-4-хидроксид-1,1-диоксидо-1-бензотиепин-5-ил]феноксид]метил]фенил]метил]-4-аза-1-азониабикло[2.2.2]октан хлорид	Лечение на първична билиарна цирроза
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-azoniabicyclo[2.2.2] oktan-chlorid	Léčbě primární biliární cirhózy
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-azoniabicyclo[2.2.2]oktanklorid	Liječenje primarne bilijarne ciroze
Danish	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylaminio)-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 <b>klorid</b>	Behandling af primær bilær cirrose
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 biliaire cirrose
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	Primaarse biliaartsirroosi 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 biliaarisen kirroosin 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 cirrhose biliaire primitive

<sup>1</sup> 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 primären biliären Zirrhose
Greek	Χλωριούχο (4R,5R)-1-[[4-[[4-[3,3-διβουτυλ-7-(διμεθυλαμινο)-2,3,4,5-τετραϋδρο-4-υδροξυ-1,1-διοξίδο-1-βενζοθειεπιν-5-yl]φαινοξυ]μεθυλ]φαινουλ]μεθυλ]-4-αζα-1-αζονιαδικυκλο[2.2.2]οκτάνιο	Θεραπεία της πρωτοπαθούς χολικής κίρρωσης
Hungarian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetil-amino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dioxid-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]oktán klorid	Primer biliaris cirrhosis kezelése
Italian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilammio)-2,3,4,5-tetraidro-4-idrossi-1,1-diossido-1-benzotiepin-5-il]fenossi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]ottano cloruro	Trattamento della cirrosi biliare primitiva
Latvian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroksi-1,1-dioksid-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]oktāna hlors	Primāras biliāras cirozes ārstēšana
Lithuanian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroksi-1,1-dioksido-1-benzotiepin-5-il]fenoksi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]oktano chloridas	Pirminės biliarinės cirozės 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 ta' ċirrozi biljari primarja
Polish	Chlorek (4R,5R)-1-[[4-[[4-[3,3-dibutylo-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroksy-1,1-dwutleno-1-benzotiepin-5-yl]fenoksy]metylo]fenylo]metylo]-4-aza-1-azoniobicyclo[2.2.2]oktanu	Leczenie pierwotnej żółciowej marskości wątroby
Portuguese	Cloreto de (4R,5R)-1-[[4-[[4-[3,3-dibutilo-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dióxido-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]octano	Tratamento da cirrose biliar primária
Romanian	Clorură de (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dioxido-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabicyclo[2.2.2]octan	Tratamentul cirozei biliare primitive

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 biliárnej cirhózy
Slovenian	(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]oktan klorid	Zdravljenje primarn2 biliarne ciroze
Spanish	Cloruro de (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetilamina)-2,3,4,5-tetrahydro-4-hidroxi-1,1-dióxido-1-benzotiepina-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]octano	Tratamiento de la cirrosis biliar 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 biliär cirrhos
Norwegian	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimetylamino)-2,3,4,5-tetrahydro-4-hydroksy-1,1-dioksido-1-benzotiepin-5-yl]fenoksy]metyl]fenyl]metyl]-4-aza-1-azoniabisyklo[2.2.2]oktanklorid	Behandling av primær biliær cirrhose
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 klóríð	Meðferð á frumkominni gallskorpulífur