



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

21 January 2014  
EMA/COMP/696783/2013 Corrigendum<sup>1</sup>  
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 Alagille syndrome

On 18 December 2013, orphan designation (EU/3/13/1214) 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 Alagille syndrome.

### What is Alagille syndrome?

Alagille syndrome is an inherited developmental disorder, caused by a mutation (defect) in the *JAG1* gene or in the *Notch2* gene, which are involved in the development of the embryo within the womb. This causes problems with early development leading to abnormalities in various parts of the body.

Most patients with this disorder have liver abnormalities resulting from having too few bile ducts. Bile ducts transport fluid called bile from the liver to the intestines, where it is used to help digest fats. Due to the reduced number of ducts, bile acids, essential components of bile, build up in the liver and damage the liver tissue as well as causing severe itching. Other common abnormalities include heart conditions such as pulmonary stenosis (narrowing of the pulmonary artery through which blood flows from the heart to the lungs), abnormally shaped bones including those of the face and spine, and abnormalities of the eye. Patients with this syndrome may have distinctive facial features such as a prominent forehead, deep-set eyes and a straight or saddle-shaped nose.

Alagille syndrome is a long-term debilitating and life-threatening disease due to liver and heart problems.

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<sup>1</sup> Correction of EC decision date, 7 September 2021.



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

At the time of designation, Alagille syndrome 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).

## **What treatments are available?**

No satisfactory methods of treatment were authorised in the EU for Alagille syndrome at the time of orphan designation. Different treatments were used to improve the functioning of the heart and to reduce the itching caused by liver disease.

## **How is this medicine expected to work?**

This 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 acid in the liver, thereby reducing the liver damage and itching seen in patients with Alagille syndrome.

## **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 Alagille syndrome had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for Alagille syndrome 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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\* 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).

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>2</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 Alagille syndrome
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 синдром на Alagille
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 Alagille syndromu
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 Alagilleovog sindroma
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 klorid	Behandling af Alagille syndrom
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 Alagille syndroom
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	Alagille sündroomi 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	Hoito Alagille oireyhtymä
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 du syndrome d'Alagille

<sup>2</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 des Alagille Syndroms
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 του συνδρόμου Alagille
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	Alagille szindróma 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 sindrome di Alagille
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	Ārstēšana Alagille sindroma
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	<i>Alagille</i> sindromo 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 tas-sindrome ta' Alagille
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 zespołu Alagille'a
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 síndrome de Alagille
Romanian	Clorură de (4R,5R)-1-[[4-[[4-[3,3-dibutil-7-(dimetilamino)-2,3,4,5-tetrahidro-4-hidroxi-1,1-dioxidio-1-benzotiepin-5-il]fenoxi]metil]fenil]metil]-4-aza-1-azoniabiciclo[2.2.2]octan	Tratamentul sindromului Alagille

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 Alagillovho syndrómu
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 sindroma Alagille
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 síndrome de Alagille
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 Alagilles syndrom
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 Alagille syndrom
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-asóniábísýkló[2.2.2]oktan klórið	Meðferð á Alagille heilkenni