



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2012
EMA/COMP/526570/2012
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid for the treatment of primary biliary cirrhosis

On 9 August 2012, orphan designation (EU/3/12/1041) was granted by the European Commission to Albireo AB, Sweden, for (2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid for the treatment of 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 pruritus (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 (an inability of the liver to work properly), and may increase the risk of liver cancer.

What is the estimated number of patients?

At the time of designation, primary biliary cirrhosis affected not more than 1.5 in 10,000 people in the European Union (EU)*. This is equivalent to a total of not more than 76,000 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 27), Norway, Iceland and Liechtenstein. This represents a population of 506,300,000 (Eurostat 2011).



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 it works in a different way to existing treatments and early studies show its effectiveness in clearing excess bile acid, particularly when used in combination with cholestyramine, a medicine used to remove bile acid from the body. 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 acids (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 (IBATs) 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 in the liver, thereby reducing the liver damage 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 medicine 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 11 July 2012 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:

Albireo AB
Arvid Wallgrens Backe 20
S-413 46 Gothenburg
Sweden
Telephone: +46 31 741 14 80
Telefax: +46 31 820223
E-mail: info@albireopharma.com

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	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro- 1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid	Treatment of primary biliary cirrhosis
Bulgarian	(2S)-2-{{[(2R)-2-[[{[3,3-дибутил-7-(метилтио)-1,1-диоксидо-5-фенил-2,3,4,5-тетрахидро-1,2,5-бензотиадиазепин-8-ил]окси}ацетил]амино]-2-(4-хидроксифенил)ацетил]амино}бутаноева киселина	Лечение на първична билиарна цирроза
Czech	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino} butanová kyselina	Léčbě primární biliární cirhózy
Danish	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino}butansyre acid	Behandling af primær biliaer cirrose
Dutch	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoïczuur	Behandeling van primaire biliaire cirrose
Estonian	(2S)-2-{{[(2R)-2-[[{[3,3-dibutüül-7-(metüülthio)-1,1-dioksido-5-fenüül-2,3,4,5-tetrahüdro-1,2,5-benzothiadiazepiin-8-üül]oksü}atsetüül]amino]-2-(4-hüdroksüfenüüll)atsetüül]amino}butaanhape	Primaarse biliaartsirroosi ravi.
Finnish	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid	Primaarisen biliaarisen kirroosin hoito
French	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(méthylthio)-1,1-dioxido-5-phényl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazépine-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphényl)acétyl]amino}butanoic acide	Traitement de la cirrhose biliaire primitive
German	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino}buttersäure	Behandlung der primären biliären Zirrhose
Greek	(2S)-2-{{[(2R)-2-[[{[3,3-διβούτυλο-7-(μεθυλθειο)-1,1-διοξειδο-5-φαινυλο-2,3,4,5-τρατραϋδρο-1,2,5-βενζοθειαδιαζεπινό-8-yl]οξύ}ακετυλο]αμινό]-2-(4-υδροξυφαινυλο)ακετυλ]αμινό}βουτανοϊκό οξύ	Θεραπεία της πρωτοπαθούς χολικής κίρρωσης
Hungarian	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(metiltio)-1,1-dioxide-5-fenil- 2,3,4,5 tetrahidro-1,2,5-benzothiadiazepin-8-il]oxi}acetil]amino]-2-(4-hidroxifenil) acetil]amino}-butánsav	Primer biliaris cirrhosis kezelése

¹ At the time of designation

Language	Active ingredient	Indication
Italian	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-diossido-5-fenil-2,3,4,5-tetraidro-1,2,5-benzotiodiazepin-8-yl]oxy}acetil)amino]-2-(4-idrossifenil)acetil}amino}acido butanoico	Trattamento della cirrosi biliare primitiva
Latvian	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl}amino}butanoic acid	Primāras biliāras cirozes ārstēšana
Lithuanian	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-dioksido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepin-8-il]oksi}acetil)amino]-2-(4-hidroksifenil)acetil}amino}sviesto rūgštis	Pirminės biliarinės cirozės gydymas
Maltese	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl}amino}butanoic acid	Kura ta' cirrozi biljari primarja
Polish	Kwas (2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metylotio)-1,1-dioksydo-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepin-8-yl]oksy}acetyl)amino]-2-(4-hydroksyfenil)acetyl}amino}butanowy	Leczenie pierwotnej żółciowej marskości wątroby
Portuguese	Ácido butanóico (2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina-8-il]oxi}acetil)amino]-2-(4-hidroxifenil)acetil}amino}	Tratamento da cirrose biliar primária
Romanian	Acid (2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepin-8-il]oxi}acetil)amino]-2-(4-hidroxifenil)acetil}amino}butanoic	Tratamentul cirozei biliare primitive
Slovak	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxypfenyl)acetyl}amino}butánová kyselina	Liečba primárnej biliárnej cirhózy
Slovenian	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-dioksido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepin-8-il]oksi}acetil)amino]-2-(4-hidroksifenil)acetil}amino}butanojka kislina	Zdravljenje primarn2 biliarne ciroze
Spanish	Ácido (2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metiltio)-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzothiadiazepin-8-il]oxi}acetil)amino]-2-(4-hidroxifenil)acetil}amino}butanoico	Tratamiento de la cirrosis biliar primaria
Swedish	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl}amino}butanoic acid	Behandling av primär biliär cirrhos
Norwegian	(2S)-2-{{(2R)-2-[[{3,3-dibutyl-7-(metyltio)-1,1-dioksido-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepin-8-yl]oksy}acetyl)amino]-2-(4-hydroksyfenyl)acetyl}amino}butansyre	Behandling av primær biliær cirrhose

Language	Active ingredient	Indication
Icelandic	(2S)-2-{[(2R)-2-[(3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl}amino}butanoic acid	Meðferð á frumkominni gallskorpulífur