28 August 2012
EMA/COMP/426291/2012
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 progressive familial intrahepatic cholestasis

On 17 July 2012, orphan designation (EU/3/12/1028) 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 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, a fluid produced by the liver called bile, which helps digestion, is not 'transported' normally to the intestine. This results in bile acids, essential components of bile, building up in liver cells and 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 chronically debilitating due to early appearance of the symptoms and liver problems. It is also life-threatening due to severe liver damage.

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 is equivalent to 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 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).

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What treatments are available?

At the time of orphan designation, no satisfactory treatments were authorised in the EU for this condition. Rifampicin was used to treat the itchiness, ursodeoxycholic acid was used to treat some types of progressive familial intrahepatic cholestasis and vitamin supplements were given to children to prevent deficiencies. Patient with end-stage liver disease underwent liver transplantation.

How is this medicine expected to work?

The medicine is expected to block some proteins on the surface of intestinal cells called 'ileal sodium-dependent bile acid transporters'. These bile acid transporters are involved in the transport of bile acids from the intestines back to the liver, where they are recycled to produce more bile, a process known as 'bile acid re-uptake'. By blocking the transporters, the medicine is expected to reduce the entry of bile acids into liver cells, and thereby prevent their accumulation and the toxicity in the liver cells. This is expected to help improve the symptoms of the disease.

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 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 13 June 2012 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[1], 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 progressive familial intrahepatic cholestasis
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 прогресивна фамилна интрахепатална холестаза
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	Léčba progresivní familiární intrahepatální cholestázy
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	Behandling af progressiv familiær intrahepatisk kolestase
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 progressieve familiale intrahepatische cholestase
Estonian	(2S)-2-{[(2R)-2-[({[3,3-dibutüül-7-(methüülthio)-1,1-dioksüido-5-fenüül-2,3,4,5-tetrahüdro-1,2,5-benzothiadiazepiin-8-üül]oksü}atsetüül)amino]-2-(4-hüdroksüfenüül)atsetüül]amino}butanoiinhape	Progresseeruva perekondliku Intrahepaatilisee kolestaasi ravi
Finnish	(2S)-2-{[(2R)-2-[({[3,3-dibutyyli-7-(metyylitio)-1,1-dioksido-5-fenyyli-2,3,4,5-tetrahydro-1,2,5-bentsotiadiatsepiini-8-yl]oksi}asetyyli)amino]-2-(4-hydroksifenyyli)asetyyli]amino}butaanihappo	Etenevän familiaalisen intrahepaattisen kolestaasin hoito
French	(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} acide butanoïque	Traitement de la cholestase intrahépatique familiale progressive

[1] At the time of designation

Language	Active ingredient	Indication
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}butanoic acid	Behandlung progressiver familiärer intrahepatischer Cholestase
Greek	(2S)-2-{[(2R)-2-[({[3,3-διβουτυλο-7-(μεθυλθειο)-1,1-διοξιδο-5-φαινυλο-2,3,4,5-τετραϋδρο-1,2,5-βενζοθειαδιαζεπαμινο-8-yl]oxy}ακετυλ)αμινο]-2-(4-υδροξυφαινυλο)ακετυλ]αμινο}βουτανοϊκό οξύ	Θεραπεία της προοδευτικής οικογενούς ενδοηπατικής χολόστασης
Hungarian	(2S)-2-{[(2R)-2-[({[3,3-dibutil-7-metiltio)-1,1-dioxid-5 fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepin-8-il]oxi}acetil)amino]-2-(4-hidroxifenil) acetil]amino}butánsav	Progresszív familiáris intrahepaticus cholestasis kezelése
Italian	(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	Trattamento della colestasi intraepatica progressiva familiare
Latvian	(2S)-2-{[(2R)-2-[({[3,3-dibutil-7-(metiltio)-1,1-dioksido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepīns-8-il]oksi}acetil)amino]-2-(4-hidroksifenil)acetil]amino}butānskābe	Progresīvās ģimenes intrahepatiskās holestāzes ārstēšana
Lithuanian	(2S)-2-{[(2R)-2-[({[3,3-dibutil-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	Progresuojančios paveldimos intrahepatinės cholestazės 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 tal-kolestasi intra-epatika li tintiret progressiva
Polish	(2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(metyltio)-1,1-dioksydo-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepin-8-yl]oksyy}acetyl)amino]-2-(4-hydroksyfenyl)acetyl]amino}butanowy kwas	Leczenie postępującej rodzinnej cholestazy wewnątrzwątrobowej
Portuguese	Ácido (2S)-2-{[(2R)-2-[({[3,3-dibutil-7-(metiltio)-1,1-dióxido-5-fenil-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina-8-il]oxi}acetil)amino]-2-(4-hidroxifenil)acetil]amino}butanoico	Tratamento da colestase intra-hepática familiar progressiva
Romanian	Acid (2S)-2-{[(2R)-2-[({[3,3-dibutil-7-(metiltio)-1,1-dioxido-5-fenil-	Tratamentul colestazei familiale intrahepatice

Language	Active ingredient	Indication
	2,3,4,5-tetrahidro-1,2,5-benzotiadiazepin-8-il]oxi}acetil)amino]-2-(4-hidroxifenil)acetil]amino}butanoic	progresive
Slovak	(2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(metyltio)-1,1-dioxido-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepín-8-yl]oxy}acetyl)amino]-2-(4-hydroxyfenyl)acetyl]amino}bután ová kyselina	Liečba progresívnej familiárnej intrahepatálnej cholestázy
Slovenian	(2S)-2-{[(2R)-2-[({[3,3-dibutil-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}maslena kislina	Zdravljenje progresivne familiarne intrahepatične holestaze
Spanish	Ácido (2S)-2-{[(2R)-2-[({[3,3-dibutil-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}butanoico	El tratamiento de la colestasis intrahepática familiar progresiva
Swedish	(2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(metyltio)-1,1-dioxido-5-fenyl-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyfenyl)acetyl]amino}butansyra	Behandling av progressiv familjär intrahepatisk kolestas
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 progressiv familiær intrahepatisk kolestase
Icelandic	(2S)-2-{[(2R)-2-[({[3,3-díbútýl-7-(methýlthíó)-1,1-díoxídó-5-phenýl-2,3,4,5-tetrahýdró- 1,2,5-benzóthíadíazepín-8-ýl]oxý}acetyýl)amínó]-2-(4-hýdróxýphenýl)acetýl]amínó}bútanóic sýra	Meðferð á ágengriættgenginni innanlifrar gallteppu