



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2012
EMA/COMP/526568/2012
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 Alagille syndrome

On 9 August 2012, orphan designation (EU/3/12/1040) 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 Alagille syndrome.

What is Alagille syndrome?

Alagille syndrome is an inherited developmental disorder, caused by a mutation in a gene (called *JAG1*) that is 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 builds up in the liver and damages the liver tissue. 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.

What is the estimated number of patients?

At the time of designation, Alagille syndrome affected not more than 0.3 in 10,000 people in the European Union (EU)*. This is equivalent to a total of not more 15,000 people, and is below the ceiling

*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).



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 at the time of orphan designation. Different treatments were used to improve the functioning of the heart and to reduce the effects of impaired liver function.

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 in the liver, thereby reducing the liver damage 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 medicine 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 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:

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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	(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 Alagille syndrome
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 синдром на Alagille
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 Alagille syndromu
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 Alagille syndrom
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 Alagille syndroom
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-hüdroksüfenüül)atsetüül]amino} butaanhape	Alagille sündroomi 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	Hoito Alagille oireyhtymä
French	(2S)-2-{{[(2R)-2-[[{[3,3-dibutyl-7-(méthylthio)-1,1-dioxido-5-phényl-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine-8-yl]oxy} acétyl)amino]-2-(4-hydroxyphényl)acétyl]amino} butanoic acide	Traitement du syndrome d'Alagille
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 des Alagille Syndroms
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]οξυ} ακετυλο]αμινό]-2-(4-υδροξυφαινυλο)ακετυλ]αμινό} βουτανοϊκό οξύ	Θεραπεία του συνδρόμου Alagille
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]oxy} acetil]amino]-2-(4-hidroxifenil) acetil]amino} butánsav	Alagille szindróma kezelése

¹ At the time of designation

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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}acido butanoico	Trattamento della sindrome di Alagille
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	Ārstēšana Alagille sindroma
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	Alagille sindromo 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 tas-sindrome ta' Alagille
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-hydroksyfenyl)acetyl]amino}butanowy	Leczenie zespołu Alagille'a
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-hidroxfenil)acetil]amino}	Tratamento da síndrome de Alagille
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-hidroxfenil)acetil]amino}butanoic	Tratamentul sindromului Alagille
Slovak	(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}butánová kyselina	Liečba Alagillovho e syndrómu
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 sindroma Alagille
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-hidroxfenil)acetil]amino}butanoico	El tratamiento de síndrome de Alagille
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 Alagilles syndrom
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 Alagille syndrom

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 syra	Meðferð á Alagille heilkenni