



European Medicines Agency  
Pre-authorisation Evaluation of Medicines for Human Use

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*Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in December 2008 on request of the Sponsor.*

## **Committee for Orphan Medicinal Products**

### **Public summary of positive opinion for orphan designation of sulfonated monophosphorylated mannose oligosaccharide for the treatment of hepatocellular carcinoma**

On 14 September 2007, orphan designation (EU/3/07/482) was granted by the European Commission to Constella Group Ltd, United Kingdom, for sulfonated monophosphorylated mannose oligosaccharide for the treatment of hepatocellular carcinoma.

#### **What is hepatocellular carcinoma?**

Tumours that begin in the liver are known as primary liver tumours. The most frequent type of primary liver tumour that has the potential to infiltrate healthy tissues (malignant) is called hepatocellular carcinoma. The most common factors known to be associated with this disease are the viral infections causing liver inflammations (hepatitis B and hepatitis C) and subsequently cirrhosis, or alcohol-induced liver cirrhosis. Hepatocellular carcinoma is a life-threatening condition.

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

At the time of designation, hepatocellular carcinoma affected approximately 1 in 10,000 people in the European Union (EU)\*. This is equivalent to a total of around 50,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

#### **What treatments are available?**

The choice of the treatment of hepatocellular carcinoma depends on several factors, mainly the stage of the disease. Treatments may include surgery, radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells), chemotherapy (using drugs to kill cancer cells) or immunotherapy (treatment by stimulation of the body's own defense system). At the time of submission of the application for orphan drug designation, several products were authorised for the condition in some Member States of the Community. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that sulfonated monophosphorylated mannose oligosaccharide might be of potential significant benefit for the treatment of hepatocellular carcinoma, because of its new mechanism of action and the possibility to use it in combination with current treatments. This assumption will have to be confirmed at the time of marketing authorisation; this will be necessary to maintain the orphan status.

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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 27), Norway, Iceland and Liechtenstein. This represents a population of 498,000,000 (Eurostat 2006).

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

Sulfonated monophosphorylated mannose oligosaccharide is structurally similar to the naturally occurring compound called heparan sulphate, which is present in the extracellular matrix (the mix of molecules between cells in tissues). For tumours to be able to grow and invade into surrounding tissues, the tumour cells have to be able to degrade heparan sulphate, and for that purpose tumour cells overexpress an enzyme called heparanase in their cell membrane.

The sponsor has suggested that the product acts by binding to this enzyme and thus inhibiting the tumour from degrading heparan sulphate and growing into to the surrounding tissues. Heparan sulphate normally also interacts with a molecule called VEGF (vascular endothelial growth factor) which stimulates the formation of blood vessels. Also, the sponsor has suggested that sulfonated monophosphorylated mannose oligosaccharide binds to VEGF and inhibits the ability of the tumour to form new blood vessels, which is critical for the survival of tumour cells.

**What is the stage of development of this medicine?**

The effects of sulfonated monophosphorylated mannose oligosaccharide were evaluated in experimental models. At the time of submission of the application for orphan designation, clinical trials in patients with sulfonated monophosphorylated mannose oligosaccharide were ongoing.

Sulfonated monophosphorylated mannose oligosaccharide was not authorised anywhere worldwide for the treatment of hepatocellular carcinoma, nor designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 25 July 2007 a positive opinion recommending the grant of the above-mentioned 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 Community) 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.

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**Translations of the active ingredient and indication in all EU languages  
and Norwegian and Icelandic**

<b>Language</b>	<b>Active Ingredient</b>	<b>Indication</b>
English	Sulfonated monophosphorylated mannose oligosaccharide	Treatment of hepatocellular carcinoma
Bulgarian	Сулфониран олигозахарид на монофосфорилирана маноза	Лечение на хепатоцелуларен карцином
Czech	Sulfonovaný monofosforylovaný oligosacharid manózy	Léčba hepatocelulárního karcinomu
Danish	Sulfoneret monofosforyleret mannose oligosaccharid	Behandling af hepatocellulært carcinoma
Dutch	Gesulfoneerd monogefosforyleerd mannose oligosaccharide	Behandeling van hepatocellulair carcinoom
Estonian	Sulfoonmonofosforülaat-mannoos-oligosahhariid	Hepatotsellulaarse kartsinoomi ravi
Finnish	Sulfonoitu monofosforyloitu mannoosi-oligosakkaridi	Hepatosellulaarisen karsinooman hoito
French	Oligosaccharide de mannose monophosphorylé sulfaté	Traitement du carcinome hépatocellulaire
German	Sulfoniertes monophosphoryliertes Mannose-Oligosaccharid	Behandlung des Leberzellkarzinoms
Greek	Ολιγοσακχαρίτης θειωμένης μονοφωσφορυλιωμένης μαννόζης	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	Szulfonált, monofoszforilált mannóz oligoszaccharid	Hepatocelluláris carcinoma kezelése
Italian	Oligosaccaride di mannosio sulfonato monofosforilato	Trattamento del carcinoma epato cellulare
Latvian	Sulfonētas monofosforilētas mannozes oligosaharīds	Hepatocellulāras karcinomas ārstēšana
Lithuanian	Sulfonintas monofosforilintas manozės oligosacharidas	Hepatoceliulinės karcinomos gydymas
Maltese	Sulfonated monophosphorylated mannose oligosaccharide	Kura tal-karċinoma epatoċellulari
Polish	Sulfonowany monofosforylowany oligosacharyd mannozy	Leczenie raka wątrobowokomórkowego
Portuguese	Oligossacarídeos de manose monofosforilados e sulfonados	Tratamento do carcinoma hepatocelular
Romanian	Oligozaharide monofosforilate și sulfonate de manoză	Tratamentul carcinomului hepatocelular
Slovak	Sulfónovaný monofosforylovaný oligosacharid manózy	Liečba hepatocelulárneho karcinómu
Slovenian	Oligosaharid sulfonirane monofosforilirane manoze	Zdravljenje hepatocelularnega karcinoma
Spanish	Oligosacárido monofosforilado sulfonatado de manosa	Tratamiento del carcinoma hepatocelular
Swedish	Sulfonerad monofosforylerad mannos oligosackarid	Behandling av hepatocellulärt karcinom
Norwegian	Sulfonert monofosforylert mannose oligosakkarid	Behandling av hepatocellulært karsinom
Icelandic	Súlfónerað einfosfórýlerað mannósaóligósakkaríð	Meðferð við lifrarfrumukrabbameini