



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid for the treatment of hepatocellular carcinoma

Please note that this product was withdrawn from the Community Register of designated orphan medicinal products in March 2011 on request of the sponsor.

On 22 October 2007, orphan designation (EU/3/07/497) was granted by the European Commission to Quintiles Ireland Ltd, Ireland, for 4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid 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 0.5 in 10,000 people in the European Union (EU)*. This is equivalent to a total of around 25,000 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?

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

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 27), Norway, Iceland and Lichtenstein. This represents a population of 498,000,000 (Eurostat 2006). This estimate is based on available information and calculations presented by the sponsor at the time of the application



high-energy rays to kill cancer cells), chemotherapy (using drugs to kill cancer cells) or immunotherapy (treatment by stimulation of the body's own defence system). At the time of submission of the application for orphan drug designation, several products were authorised for the condition in some countries of the Community. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that 4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid might be of potential significant benefit for the treatment of hepatocellular carcinoma, because it might improve the long-term outcome of the patients. This assumption will have to be confirmed at the time of marketing authorisation; this will be necessary to maintain the orphan status.

How is this medicine expected to work?

4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid is structurally similar to a class of compounds called retinoids. Retinoids can pass in and out of the cells of the body freely. Inside the cells they bind to receptors and form complexes that can influence the suppression or expression of specific genes. The sponsor has suggested that the mechanism of action of 4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid is that through these complexes it suppresses some genes that are necessary for tumour cells to grow and increases the expression of other genes that cause the tumour cells to destruct.

What is the stage of development of this medicine?

The effects of 4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with 4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid were ongoing.

4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid was not authorised anywhere worldwide for the treatment of hepatocellular carcinoma or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 12 September 2007 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	4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid	Treatment of hepatocellular carcinoma
Bulgarian	4-[3,5-бис(триметилсилил)бензамидо] бензоева киселина	Лечение на хепатоцелуларен карцином
Czech	kyselina 4-[3,5-bis(trimethylsilyl)benzamido] benzoová	Léčba hepatocelulárního karcinomu
Danish	4-[3,5-bis(trimethylsilyl)benzamid] Benzoesyre	Behandling af hepatocellulært carcinom
Dutch	4-[3,5-bis(trimethylsilyl)benzamido]benzoëzuur	Behandeling van hepatocellulair carcinoom
Estonian	4-[3,5-bis(trimetüülsilüül)bensamiid]bensoehape	Hepatotsellulaarse kartsinoomi ravi
Finnish	4-[3,5-bis(trimetyylisilyyli)bentsamido] Bentsoehappo	Hepatosellulaarisen karsinooman hoito
French	Acide benzoïque 4-[3,5-bis(triméthylsilyl)benzamido]	Traitement du carcinome hépatocellulaire
German	4-[3,5-bis(trimethylsilyl)benzamido] Benzoessäure	Behandlung des Leberzellkarzinoms
Greek	4-[3,5-δισ(τριμεθυλοσιλυλ)-βενζαμιδο] βενζοϊκό οξύ	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	4-[3,5-bisz(trimetil-szilil)-benzamido] benzoesav	Hepatocelluláris carcinoma kezelése
Italian	Acido 4-[3,5-bis(trimetilsilil)benzammido] benzoico	Trattamento del carcinoma epatocellulare
Latvian	4-[3,5-bis(trimetilsilil)benzamido] benzoskābe	Hepatocellulāras karcinomas ārstēšana
Lithuanian	4-[3,5-bis(trimetilsilil)benzamido] benzoinė rūgštis	Hepatoceliulinės karcinomos gydymas
Maltese	4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid	Kura tal-karċinoma epatoċellulari
Polish	Kwas 4-[3,5-bis(trimetylosililo)benzamido] benzoesowy	Leczenie raka wątrobowokomórkowego
Portuguese	Ácido 4-[3,5-bis(trimetilsilil)benzamido] benzoico	Tratamento do carcinoma hepatocelular
Romanian	Acid 4-[3,5-bi(trimetilsilil)benzoamido] benzoic	Tratamentul carcinomului hepatocelular
Slovak	Kyselina 4-[3,5-bis(trimetylsilyl)benzamino] benzoová	Liečba hepatocelulárneho karcinómu
Slovenian	4-[3,5-bis(trimetilsilil)benzamido] benzojska kislina	Zdravljenje hepatocelularnega karcinoma
Spanish	Ácido 4-[3,5-bis(trimetilsilil)benzamido] benzoico	Tratamiento del carcinoma hepatocelular
Swedish	4-[3,5-bis(trimetylsilyl)benzamido] benzoesyra	Behandling av hepatocellulärt carcinom

¹ At the time of designation

Language	Active Ingredient	Indication
Norwegian	4-[3,5-bis(trimetylsilyl)benzamido] benzosyre	Behandling av hepatocellulært karsinom
Icelandic	4-[3,5-bis(trímetylsilýl)bensamídó] bensósýra	Meðferð við lifrarfrumukrabbameini