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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF

4-Amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinone for the treatment of hepatocellular carcinoma

On 14 September 2007, orphan designation (EU/3/07/477) was granted by the European Commission to Interface International Consultancy Ltd, UK, for 4-Amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinone for the treatment of hepatocellular carcinoma.

What is hepatocellular carcinoma?

Tumours that begin in the liver are known as liver tumours. Liver tumours that originate from the specific cells of the liver (hepatocytes) are called hepatocellular carcinomas. The most common factors known to be associated with this disease are viral infections that result in liver inflammation (in particular, hepatitis B and hepatitis C) and cirrhosis of the liver, particularly if induced by excessive consumption of alcohol. Hepatocellular carcinoma is a life-threatening condition.

What are the methods of treatment available?

Several medicinal products were authorised in the European Union for the treatment of hepatocellular carcinoma, at the time of the application. Surgical removal of the tumour or liver transplantation are the only chances of a cure, but are possible or indicated only in a very limited number of patients. The medicinal product is expected to offer a potential significant benefit over existing authorised treatments as it has a different mechanism of action. The assumption of significant benefit will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

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

According to the information provided by the sponsor, hepatocellular carcinoma was considered to affect about 50,000 persons in the European Union.

How is this medicinal product expected to act?

The product is a prodrug (a drug precursor), which means that it is not active alone, but it is converted by the human body into the active substance, in this case into cytarabine monophosphate that is further converted to cytarabine triphosphate. Cytarabine triphosphate inhibits the growth of many tumours, but it is not normally used in the treatment of liver tumours because it is toxic for the bone marrow. 4-Amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinone is designed to bypass the bone marrow, because as a precursor, it would undergo conversion initially to cytarabine monophosphate and ultimately cytarabine

* 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.

triphosphate only in the liver, and not in other tissues, including the bone marrow where most of the toxicity occurs.

What is the stage of development of this medicinal product?

The effects of the medicinal product were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with hepatocellular carcinoma were ongoing.

The medicinal product was not authorised anywhere in the world for hepatocellular carcinoma, nor designated as orphan medicinal product for this condition, at the time of submission of the application.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 24 July 2007 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which were considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

For more information:

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

Language	Active Ingredient	Indication
English	4-Amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinone	Treatment of hepatocellular carcinoma
Bulgarian	4-амино-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-оксидо-4-(4-пиридинил)-1,3,2-диоксафосфоринан-2-yl]-β-D-арабинофуранозил]-2(1 <i>H</i>)-пиримидинон	Лечение на хепатоцелуларен карцином
Czech	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxafosforinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinon	Léčba hepatocelulárního karcinomu
Danish	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinon	Behandling af hepatocellulært carcinom
Dutch	4-Amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxafosforinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinon	Behandeling van hepatocellulair carcinoom
Estonian	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oksido-4-(4-püridinüül)-1,3,2-dioksafosforinaan-2-üül]-β-D-arabinofuranosüül]-2(1 <i>H</i>)-pürimidinon	Hepatotsellulaarse kartsinoomi ravi
Finnish	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oksido-4-(4-pyridinyyli)-1,3,2-dioksafosforinan-2-yyli]-β-D-arabinofuranosyyli]-2(1 <i>H</i>)-pyrimidinoni	Hepatosellulaarisen karsinooman hoito
French	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxydo-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinone	Traitement du carcinome hépatocellulaire
German	4-Amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1 <i>H</i>)-pyrimidinon	Behandlung des Leberzellkarzinoms
Greek	4-αμινο-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-οξίδο-4-(4-πυριδινυλ-1,3,2-διοξαφωσφοριναν-2-yl)-β-D-αραβινοφουρανοσυλ]-2(1 <i>H</i>)-πυριμιδινόνη	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oxido-4-(4-piridinil)-1,3,2-dioxa-foszfórínán-2-il]-β-D-arabinofuranozil]-2(1 <i>H</i>)-pirimidinon	Hepatocelluláris carcinoma kezelése
Italian	4-Ammino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-ossido-4-(4-piridinil)-1,3,2-diossafosforinan-2-il]-β-D-arabinofuranosil]-2(1 <i>H</i>)-pirimidinone	Trattamento del carcinoma epatocellulare
Latvian	4-amino-1-[5- <i>O</i> -[(2 <i>R</i> ,4 <i>S</i>)-2-oksido-4-(4-piridinil)-1,3,2-dioksafosforinan-2-il]-β-D-arabinofuranozil]-2(1 <i>H</i>)-pirimidinons	Hepatocellulārs karcinomas ārstēšana

Lithuanian	4-amino-1-[5-O-[(2R,4S)-2-oksido-4-(4-piridinil)-1,3,2-dioksafosforinan-2-il]-β-D-arabinofuranosil]-2(1H)-pirimidinonas	Hepatoceliulinės karcinomos gydymas
Maltese	4-Amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinone	Kura tal-karcinoma epatoċellulari
Polish	4-Amino-1-[5-O-[(2R,4S)-2-oksydo-4-(4-pirydynylo)-1,3,2-dioksafosforynan-2-ylo]-β-D-arabinofuranozylo]-2(1H)-pirymidynon	Leczenie raka wątrobowokomórkowego
Portuguese	4-Amino-1-[5-O-[(2R,4S)-2-óxido-4-(4-piridinil)-1,3,2-dioxafosforinana-2-il]-β-D-arabinofuranosil]-2(1H)-pirimidinona	Tratamento do carcinoma hepatocelular
Romanian	4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-piridinil)-1,3,2-dioxafosforinan-2-yl]-β-D-arabinofuranozil]-2(1H)-pirimidinona	Tratamentul carcinomului hepatocelular
Slovak	4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxafosforinán-2-yl]-β-D-arabinofuranozyl]-2(1H)-pyrimidinón	Liečba hepatocelulárneho karcinómu
Slovenian	4-amino-1-[5-O-[(2R,4S)-2-oksido-4-(4-piridinil)-1,3,2-dioksafosforinan-2-il]-β-D-arabinofuranozil]-2(1H)-pirimidinon	Zdravljenje hepatocelularnega karcinoma
Spanish	4-Amino-1-[5-O-[(2R,4S)-2-óxido-4-(4-piridinil)-1,3,2-dioxafosforinan-2-il]-β-D-arabinofuranosil]-2(1H)-pirimidinona	Tratamiento del carcinoma hepatocelular
Swedish	4-amin-1-[5-O-[(2R,4S)-2-oxid-4-(4-pyridinyl)-1,3,2-dioxafosforinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinon	Behandling av hepatocellulärt karcinom
Norwegian	4-amino-1-[5-O-[(2R,4S)-2-oksido-4-(4-pyridinyl)-1,3,2-dioksafosforinan-2-yl]-β-D-arabinofuranosyl]-2(1H)-pyrimidinon	Behandling av hepatocellulært karsinom
Icelandic	4-amínó-1-[5-O-[(2R,4S)-2-oxídó-4-(4-pýridínýl)-1,3,2-díoxafosfórínan-2-ýl]-β-D-arabínófúranósýl]-2(1H)-pýrimídínón	Meðferð við lifrarfrumukrabbameini