



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideneaminoxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinoline-3, 14-(4H, 12H)-dione, hydrochloride for the treatment of hepatocellular carcinoma

On 1 October 2010, orphan designation (EU/3/10/788) was granted by the European Commission to TLC Biopharmaceuticals B.V., the Netherlands, for (S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideneaminoxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinoline-3, 14-(4H, 12H)-dione, hydrochloride for the treatment of hepatocellular carcinoma.

What is hepatocellular carcinoma?

Hepatocellular carcinoma is a primary cancer of the liver (a cancer that starts in the liver, rather than a cancer that has spread to the liver from another location in the body). It is more common in men than in women, and occurs mostly in people who have scarring of the liver (cirrhosis) or after infection with the hepatitis B or C viruses. Symptoms of the disease include pain and swelling in the tummy, weight loss, weakness, loss of appetite and nausea (feeling sick).

Hepatocellular carcinoma is a severe and life-threatening disease that is associated with very poor long-term survival.

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 51,000 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 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 506,500,000 (Eurostat 2010).



What treatments are available?

At the time of designation, several medicines were authorised in the EU for the treatment of hepatocellular carcinoma. The choice of treatment depended mainly on how advanced the disease was. Surgery to remove the tumour and liver transplantation were the only ways to cure the cancer, but could only be used in very few patients. Other treatments included radiotherapy (treatment with radiation), chemotherapy (medicines to treat cancer) and immunotherapy (medicines that stimulate the immune system to kill the cancer cells).

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with hepatocellular carcinoma because early studies show that it might improve the treatment of patients with this condition. This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

This anticancer medicine belongs to the group 'topoisomerase inhibitors'. It is expected to work mainly by blocking an enzyme called topoisomerase I, which is involved in the division of DNA. When the enzyme is blocked, the DNA strands break. This prevents the cancer cells from dividing and they eventually die.

What is the stage of development of this medicine?

The effects of this medicine have been evaluated in experimental models.

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

At the time of submission, this medicine was not authorised anywhere in the EU for hepatocellular carcinoma 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 8 July 2010 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	(S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideneaminoxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinoline-3, 14-(4H, 12H)-dione, hydrochloride	Treatment of hepatocellular carcinoma
Bulgarian	(S)-10-[(диметиламино)метил]-4-етил-9-хидроксид-4-О-[алфа-(2'', 4'', 5'', 7''-тетранитро-9''-флуоренилиденаминоокси)пропионил]-1H-пирано[3', 4', 6', 7']индолизин[1,2-бета]-квинолин-3, 14-(4H, 12H)-дион, хидрохлорид	Лечение на хепатоцелуларен карцином
Czech	(S)-10-[(dimethylamino)metyl]-4-etyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideneaminoxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-chinolin-3, 14-(4H, 12H)-dion, hydrochlorid	Léčba hepatocelulárního karcinomu
Danish	(S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideneaminoxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinolin-3, 14-(4H, 12H)-dion, hydrochlorid	Behandling af hepatocellulært carcinom
Dutch	(S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylideenamino-oxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2-beta]-chinoline-3, 14-(4H, 12H)-dion, hydrochloride	Behandeling van hepatocellulair carcinoom
Estonian	(S)-10-[(dimetüülamino)metüül]-4-etüül-9-hüdroksü-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenüliideenaminoooksü)propionüül]-1H-pürano[3', 4', 6', 7']indolisiin[1,2-beta]-kinoliin-3, 14-(4H, 12H)-dioon, hüdroksükloriid	Hepatotsellulaarse kartsinoomi ravi
Finnish	(S)-10-[(dimetyyliamino)metyyli]-4-etyyli-9-hydroksi-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenyyliidenamino-oksi)propionyyli]-1H-pyrano[3', 4', 6', 7']indolitsino[1,2-beta]-kinoliini-3, 14-(4H, 12H)-dioni, hydrokloridi	Hepatosellulaarisen karsinooman hoito
French	Chlorhydrate de (S)-10-[(diméthylamino)méthyl]-4-éthyl-9-hydroxy-4-O-[alpha-(2'', 4'', 5'', 7''-tétranitro-9''-fluorénylidène-amino-oxy)propionyl]-1H-pyrano[3', 4', 6', 7']indolizino[1,2- bêta]-quinoline-3, 14-(4H, 12H)-dione	Traitement du carcinome hépatocellulaire

¹ At the time of designation

German	(S)-10-[(Dimethylaminomethyl)-4-ethyl-9-hydroxy-4-O-[alpha-(2", 4", 5", 7"-tetranitro-9"-fluorenylideneaminoxy)propionyl]-1 <i>H</i> -pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinolin-3, 14-(4 <i>H</i> ,12 <i>H</i>)-dion, hydrochlorid	Behandlung des Leberzellkarzinoms
Greek	Υδροχλωρική (S)-10-[(διμεθυλαμινο)μεθυλο]-4-αιθυλο-9-υδροξυ-4-O-[α-(2", 4", 5", 7"-τετρανιτρο-9"-φθορενυλιδενοαμινοοξυ)προπιονυλο]-1 <i>H</i> -πυρανο[3', 4', 6', 7']ινδολιζινο[1,2-β]-κινολινο-3, 14-(4 <i>H</i> , 12 <i>H</i>)-διόνη	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	(S)-10-[dimetilamino)metil]-4-etil-9-hidroxi-4-O-[alpha-(2",4",5",7"-tetranitro-9"-fluorenilidinaminooxi)propionil]-1 <i>H</i> -pirano[3',4',6',7']indolizino[1,2-beta]-kinolin-3,14-(4 <i>H</i> ,12 <i>H</i>)-dion, hidroklorid	Hepatocelluláris carcinoma kezelése
Italian	Cloridrato di (S)-10-[(dimetilamino)metil]-4-etil-9-idrossi-4-O-[alpha-(2", 4", 5", 7"-tetranitro-9"-fluorenilidenamminoossi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizino[1,2-beta]-chinolin-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dione	Trattamento del carcinoma epatocellulare
Latvian	(S)-10-[(dimetilamino)metil]-4-etil-9-hidroksi-4-O-[alpha-(2", 4", 5", 7"-tetranitro-9"-fluorenilideneaminooksi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizīn[1,2-beta]-hinolīn-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dions, hidrohlorīds	Hepatocellulāras karcinomas ārstēšana
Lithuanian	(S)-10-[(dimetilamino)metil]-4-etil-9-hidroksi-4-O-[alfa-(2", 4", 5", 7"-tetranitro-9"-fluorenilideneaminooksi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizino[1,2-beta]-kvinolino-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dionas	Hepatoceliulinės karcinomos gydymas
Maltese	(S)-10-[(dimethylamino)methyl]-4-ethyl-9-hydroxy-4-O-[alpha-(2", 4", 5", 7"-tetranitro-9"-fluorenylideneaminoxy)propionyl]-1 <i>H</i> -pyrano[3', 4', 6', 7']indolizino[1,2-beta]-quinoline-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dione, hydrochloride	Kura tal-karċinoma epatoċellulari
Polish	(S)-10-[(dimetyloamino)metylo]-4-etylo-9-hydroksy-4-O-[alfa-(2", 4", 5", 7"-tetranitro-9"-fluorenylidenaminoooksy)propionylo]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizyno[1,2-beta]-chinolino-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dion, chlorowodorek	Leczenie raka wątrobowokomórkowego
Portuguese	Cloridrato de (S)-10-[(dimetilamino)metil]-4-etil-9-hidroxi-4-O-[alpha-(2", 4", 5", 7"-tetranitro-9"-fluorenilidenoaminooxi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizino[1,2-beta]-quinolina-3, 14-(4 <i>H</i> , 12 <i>H</i>)-diona	Tratamento do carcinoma hepatocelular

Romanian	Clorhidrat de (S)-10-[(dimetilamino)metil]-4-etil-9-hidroxi-4-O-[alfa-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenilidenaminooxi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizin[1,2-beta]-chinolină-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dionă	Tratamentul carcinomului hepatocelular
Slovak	Chlorid (S)-10-[(dimetylaminometyl)-4-etyl-9-hydroxy-4-O-[alfa-(2'', 4'', 5'', 7''-tetranitro-9''-fluórenylideneaminooxy)propionyl]-1 <i>H</i> -pyrano[3', 4', 6', 7']indolizino[1,2-beta]-chinolín-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dión	Liečba hepatocelulárneho karcinómu
Slovenian	(S)-10-[(dimetilamino)metil]-4-etil-9-hidroksi-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenilidenaminooksi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizino[1,2-beta]-kvinolin-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dion, hidroklorid	Zdravljenje hepatocelularnega karcinoma
Spanish	Clorhidrato de (S)-10-[(dimetilamino)metil]-4-etil-9-hidroxi-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenilidenoaminooxi)propionil]-1 <i>H</i> -pirano[3', 4', 6', 7']indolizino[1,2-beta]-quinolina-3, 14-(4 <i>H</i> , 12 <i>H</i>)-diona	Tratamiento del carcinoma hepatocelular
Swedish	(S)-10-[(dimetylaminometyl)-4-etyl-9-hydroxi-4-O-[alpha-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylidenaminooxi)propionyl]-1 <i>H</i> -pyrano[3', 4', 6', 7']indolizin[1,2-beta]-kinolin-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dion, hydroklorid	Behandling av hepatocellulärt karcinom
Norwegian	(S)-10-[(dimetylaminometyl)-4-etyl-9-hydroksy-4-O-[alfa-(2'', 4'', 5'', 7''-tetranitro-9''-fluorenylidenaminooksy)propionyl]-1 <i>H</i> -pyrano[3', 4', 6', 7']indolizino[1,2-beta]-kinolin-3, 14-(4 <i>H</i> , 12 <i>H</i>)-dion, hydroklorid	Behandling av hepatocellulært karsinom
Icelandic	(S)-10-[(dímetýlamínó)metýl]-4-etýl-9-hýdroxý-4-O-[alpha-(2'', 4'', 5'', 7''-tetranítró-9''-flúorenýlídenamínóoxý)própíónýl]-1 <i>H</i> -pýranó[3', 4', 6', 7']indólízínó[1,2-beta]-kínólín-3, 14-(4 <i>H</i> , 12 <i>H</i>)-díón, hydróklóríð	Meðferð við lifrarfrumukrabbameini