



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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EMA/COMP/95768/2013  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate for the treatment of hepatocellular carcinoma

On 12 March 2013, orphan designation (EU/3/13/1109) was granted by the European Commission to Eli Lilly Nederland B.V., The Netherlands, for 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate 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 elsewhere 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 abdomen, weight loss, weakness, loss of appetite and nausea (feeling sick).

Hepatocellular carcinoma is a serious and life-threatening illness that is associated with poor overall 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 was equivalent to a total of around 51,000 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?

At the time of designation, some patients with early stage hepatocellular carcinoma were treated with surgery to remove part of the liver. Chemotherapy (medicines to treat cancer) was generally used after surgery or on its own if surgery was not possible or the disease had spread to other parts of the

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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 509,000,000 (Eurostat 2013).



body (metastatic disease). Several chemotherapy medicines were authorised in the EU for use in hepatocellular carcinoma, such as doxorubicin, epirubicin, fluorouracil, mitomycin, mitoxantrone and sorafenib.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with hepatocellular carcinoma because early studies show that it may delay the progression of the disease in patients whose disease has stopped responding to, or is resistant to, other authorised treatments. 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?**

The medicine is expected to work by blocking receptors on the surface of cells that are activated by a substance called transforming growth factor beta (TGF- $\beta$ ), which has an important role in the growth of tissue. In advanced, metastatic cancers, including hepatocellular carcinoma, TGF- $\beta$  promotes the progression of the cancer. By blocking the receptors for TGF- $\beta$ , this medicine is expected to delay the progression of hepatocellular carcinoma.

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

The effects of the medicinal product have been evaluated in experimental models.

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

At the time of submission, the medicinal product 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 6 February 2013 recommending the granting of this 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 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 languages<sup>1</sup>, Norwegian and Icelandic

Language	Active ingredient	Indication
English	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate	Treatment of hepatocellular carcinoma
Bulgarian	4-[2-(6-метилпиридин-2-ил)-5,6-дихидро-4H-пироло[1,2-б]пиразол-3-ил]-хинолин-6-карбоксамид монохидрат	Лечение на хепатоцелуларен карцином
Czech	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrol-[1,2-b]pyrazol-3-yl]-chinolin-6-karboxamid monohydrát	Léčba hepatocelulárního karcinomu
Danish	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-6-carboxamid monohydrat	Behandling af hepatocellulært karcinom
Dutch	4-[2-(6-methylpyridine-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-chinoline-6-carboxamide monohydraat	Behandeling van hepatocellulair carcinoom
Estonian	4-[2-(6-metüülpüridiin-2-üül)-5,6-dihüdro-4H-pürrolo[1,2-b]pürasool-3-üül]-kinoliin-6-karboß ksamiid monohüdraat	Hepatosellulaarse kartsinoomi ravi
Finnish	4-[2-(6-metyyliipyridiini-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyratsoli-3-yl]-kinoliini-6-karboksamidi monohydraatti	Hepatosellulaarisen karsinooman hoito
French	4-[2-(6-méthylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole-3-yl]-quinoline-6-carboxamide monohydraté	Traitement du cancer hépatocellulaire
German	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-6-carboxamidmonohydrat	Behandlung des Leberzellkarzinoms
Greek	4-[2-(6-μεθυλοπυριδιν-2-υλο)-5,6-δι-υδρο-4H-πυρολο[1,2-β]πυραζολ-3-υλο]-κινολίνη-6-μονοϋδρικο καρβοξαμίδιο	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	4-[2-(6-metilpiridin-2-il)-5,6-dihidro-4H-pirrolo[1,2-b]pirazol-3-il]-kinolin-6-karboxamid monohidrát	Hepatocellularis carcinoma kezelése
Italian	4-[2-(6-metilpiridin-2-il)-5,6-deidro-4H-pirrolo[1,2-b]pirazol-3-il]-chinolin-6-carbossamide monoidrato	Trattamento del carcinoma epatocellulare
Latvian	4-[2-(6-metilpiridīn-2-il)-5,6-dihidro-4H-pirrolo[1,2-b]pirazol-3-il]-kvinolin-6-karboksamīda monohidrāts	Hepatocellulāras karcinomas ārstēšana
Lithuanian	4-[2-(6-metilpiridin-2-il)-5,6-dihidro-4H-pirolol[1,2-b]pirazol-3-il]-kvinolino-6-karboksamido monohidratas	Hepatoceliulinės karcinomos gydymas

<sup>1</sup> At the time of designation

Language	Active ingredient	Indication
Maltese	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pirazol-3-yl]-quinoline-6-carboxamide monohydrate	Kura tal-karċinoma epatoċellulari
Polish	4-[2-(6-metylopirydyn-2-ylo)-5,6-dihydro-4H-pirololo[1,2-b]pirazol-3-ilo]-chinolino-6-karboksyamid jednowodny	Leczenie raka wątrobowokomórkowego
Portuguese	4-[2-(6-metilpiridina-2-il)-5,6-dihidro-4H-pirrololo[1,2-b]pirazol-3-il]-quinolina-6-carboxamida mono-hidratada	Tratamento do carcinoma hepatocelular
Romanian	4-[2-(6-metilpridin-2-yl)-5,6-dihidro-4H-pirrololo[1,2-b]pirazol-3-il]-quinolin-6-carboxamid monohidrat	Tratamentul carcinomului hepatocelular
Slovak	Monohydrát 4-[2-(6-metylpyridín-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pirazol-3-yl]-chinolín-6-karboxamidu	Liečba hepatocelulárneho karcinómu
Slovenian	4-[2-(6-metilpiridín-2-il)-5,6-dihidro-4H-pirololo[1,2-b]pirazol-3-il]-kinolin-6-karboksamid monohidrat	Zdravljenje hepatocelularnega karcinoma
Spanish	4-[2-(6-metilpiridina-2-il)-5,6-dihidro-4H-pirrololo [1,2-b] pirazol-3-il]-quinolina-6-carboxamida monohidrato	Tratamiento del carcinoma hepatocelular
Swedish	4-[2-(6-metylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pirazol-3-yl]-kinolin-6-karboxamidmonohydrat	Behandling av hepatocellulärt karcinom
Norwegian	4-[2-(6-metylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pirazol-3-yl]-kinolin-6-karboksamid monohydrate	Behandling av hepatocellulært karsinom
Icelandic	4-[2-(6-metylpyridín-2-ýl)-5,6-tvíhýdró-4H-pýrróló[1,2-b]pýrazól-3-ýl]-kínólín-6-karboxamíð einhýdrat	Meðferð við lifrarfrumukrabbameini