



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-[4-(3-amino-1H-indazol-4 yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea
for the treatment of hepatocellular carcinoma

On 20 December 2007, orphan designation (EU/3/07/517) was granted by the European Commission to Abbott Laboratories Limited, United Kingdom, for N-[4-(3-amino-1H-indazol-4 yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea for the treatment of hepatocellular carcinoma.

The sponsorship was transferred to AbbVie Ltd, United Kingdom, in February 2013.

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 2.7 in 10,000 people in the European Union (EU). This was equivalent to a total of around 135,000 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 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

*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. At the time of designation, this represented a population of 500,300,000 (Eurostat 2007).



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 N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea might be of potential significant benefit for the treatment of hepatocellular carcinoma, because it might improve the long-term outcome of the patients. The 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?

N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea is a chemically synthesised product. The sponsor suggested the mechanism of action of N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea on hepatocellular carcinoma would consist in preventing the formation of new blood vessels within the tumour, since these are critical for the survival of the cancer cells.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the effects of N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea had been evaluated in experimental models, while, clinical trials in patients with hepatocellular carcinoma were ongoing.

N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea was not authorised anywhere in the world for the treatment of hepatocellular carcinoma, at the time of submission.

Orphan designation of N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea had already been granted in the United States for the condition.

In accordance with Regulation (EC) No 1411/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 November 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	N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea	Treatment of hepatocellular carcinoma
Bulgarian	N-[4-(3-амино-1H-индазол-4-ил)фенил]-N'-(2-флуоро-5-метилфенил) уреа	Лечение на хепатоцелуларен карцином
Czech	N-[4-(3-amino-1H-indazol-4-yl)fenyl]-N'-(2-fluor-5-methylfenyl) močovina	Léčba hepatocelulárního karcinomu
Danish	N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea	Behandling af hepatocellulært carcinom
Dutch	N-[4-(3-amino-1H-indazol-4-yl)fenyl]-N'-(2-fluoro-5-methylfenyl)-ureum	Behandeling van hepatocellulair carcinoom
Estonian	N-[4-(3-amino-1H-indasool-4-üül)fenüül]-N'-(2-fluoro-5-metüülfenüül) uurea	Hepatotsellulaarse kartsinoomi ravi
Finnish	N-[4-(3-amino-1H-indatsoli-4-yl)fenyyli]-N'-(2-fluoro-5-metyylifenyyli) urea	Hepatosellulaarisen karsinooman hoito
French	N-[4-(3-amino-1H-indazol-4-yl)phényl]-N'-(2-fluoro-5-méthylphényl) urée	Traitement du carcinome hépatocellulaire
German	N-(4-(3-amino-1H-indazol-4yl)phenyl)-N'-(2-fluoro-5-methylphenyl)-Harnstoff	Behandlung des Leberzellkarzinoms
Greek	N-[4-(3-αμινo-1H-ινδαζολ-4-υλ)φαινυλ]-N'-(2-φθορο-5-μεθυλοφαινυλ) ουρία	Θεραπεία του ηπατοκυτταρικού καρκινώματος
Hungarian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluor-5-metilfenil) karbamid	Hepatocelluláris carcinoma kezelése
Italian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluoro-5-metilfenil) urea	Trattamento del carcinoma epatocellulare
Latvian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluor-5-metilfenil) urīnviela	Hepatocellulāras karcinomas ārstēšana
Lithuanian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluoro-5-metilfenil) karbamidas	Hepatoceliulinės karcinomos gydymas
Maltese	N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl) urea	Kura tal-karċinoma epatoċellulari
Polish	N-[4-(3-amino-1H-indazolo-4-yl)fenylo]-N'-(2-fluoro-5-metylofenylo) mocznik	Leczenie raka wątrobowokomórkowego
Portuguese	N-[4-(3-amino-1H-indazol-4-il) fenil]-N'-(2-flúor-5-metilfenil) ureia	Tratamento do carcinoma hepatocelular
Romanian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluoro-5-metilfenil) uree	Tratamentul carcinomului hepatocelular
Slovak	N-[4-(3-amino-1H-indazol-4-yl)fenyl]-N'-(2-fluór-5-metylfenyl)močovina	Liečba hepatocelulárneho karcinómu
Slovenian	N-[4-(3-amino-1H-indazol-4-il)fenil]-N'-(2-fluoro-5-metilfenil) urea	Zdravljenje hepatocelularnega karcinoma

¹ At the time of designation

Language	Active Ingredient	Indication
Spanish	N-[4-(3-amino-1H-indazol-4-yl)fenil]-N'-(2-fluoro-5-metilfenil) urea	Tratamiento del carcinoma hepatocelular
Swedish	N-[4-(3-amino-1H-indazol-4-yl)fenyl]-N'-(2-fluor-5-metylfenyl) urea	Behandling av hepatocellulärt karcinom
Norwegian	N-[4-(3-amino-1H-indazol-4-yl)fenyl]-N'-(2-fluoro-5-metylfenyl) urea	Behandling av hepatocellulært karsinom
Icelandic	N-[4-(3-amínó-1H-indazól-4 ýl)fenýl]-N'-(2-flúoró-5-metýlfenýl) þvagefni	Meðferð við lifrarfrumukrabbameini