

16 October 2017  
EMA/557429/2017

## Public summary of opinion on orphan designation

N-{2-[(6-{[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide for the treatment of hepatocellular carcinoma

On 23 August 2017, orphan designation (EU/3/17/1902) was granted by the European Commission to Eisai Europe Limited, United Kingdom, for N-{2-[(6-{[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide (also known as H3B-6527) 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 one 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 liver scarring (cirrhosis), or after hepatitis B or C infection. Features of the disease include yellow skin, pain and swelling in the abdomen, easy bruising, weight loss, weakness, loss of appetite and nausea.

Hepatocellular carcinoma is long-term debilitating and life threatening, with patients surviving on average for a few months or years after diagnosis.

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

At the time of designation, hepatocellular carcinoma affected approximately 1.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 77,000 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, liver transplantation or radiofrequency ablation (directing heat and

\*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 28), Norway, Iceland and Liechtenstein. This represents a population of 515,700,000 (Eurostat 2017).

electricity through a needle to destroy cancer cells). Chemotherapy (medicines to treat cancer) was used if surgery was not possible or the disease had spread to other parts of the body (metastatic disease). Nexavar (sorafenib) was authorised in the EU for use in hepatocellular carcinoma.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with hepatocellular carcinoma. This is because early laboratory studies indicated that it blocked tumour growth more than the currently authorised product. 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 medicine blocks the activity of a receptor (target) on the surface of cells called fibroblast growth factor receptor 4 (FGFR4). In hepatocellular carcinoma, FGFR4 is overactive and is involved in the growth of cancer cells. By blocking FGFR4, this medicine is expected to prevent or slow down the growth of the cancer.

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

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

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

At the time of submission, the 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 13 July 2017 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's [rare disease designations page](#).

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   | N-{2-[(6-{[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide             | Treatment of hepatocellular carcinoma     |
| Bulgarian | N-{2-[(6-{[(2,6-дихлоро-3,5-диметоксифенил)карбамоил](метил)амино}пиримидин-4-ил)амино]-5-(4-етилпиперазин-1-ил)фенил}проп-2-енамид                   | Лечение на хепатоцелуларен карцином       |
| Croatian  | N-{2-[(6-{[(2,6-dikloro-3,5-dimetoksifenil)karbamoil](metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamid                   | Liječenje hepatocelularnog karcinoma      |
| Czech     | N-{2-[(6-{[(2,6-dikloro-3,5-dimetoksifenil)karbamoil](metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamid                   | Léčba hepatocelulárního karcinomu         |
| Danish    | N-{2-[(6-{[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamid              | Behandling af hepatocellulært karcinom    |
| Dutch     | N-{2-[(6-{[(2,6-dichloor-3,5-dimethoxyfenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)fenyl}prop-2-enamide               | Behandeling van hepatocellulair carcinoom |
| Estonian  | N-{2-[(6-{[(2,6-dikloro-3,5-dimetoksüfenüül)karbamoüül](metüül)amino}pürimidiin-4-üül)amino]-5-(4-etüülpiperasiin-1-üül)fenüül}prop-2-eenamiid        | Hepatotsellulaarse kartsinoomi ravi       |
| Finnish   | N-{2-[(6-{[(2,6-dikloori-3,5-dimetoksifenyyli)karbamoyyli](metyyli)amino}-pyrimidin-4-yyli)amino]-5-(4-etyylipiperatsin-1-yyli)fenyyli}prop-2-enamidi | Hepatosellulaarisen karsinooman hoito     |
| French    | N-{2-[(6-{[(2,6-dichloro-3,5-diméthoxyphényl)carbamyle](méthylamino}pyrimidine-4-yl)amino]-5-(4-éthylpipérazine-1-yl)phényl}prop-2-énamide            | Traitement du cancer hépatocellulaire     |
| German    | N-{2-[(6-{[(2,6-Dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino}pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamid              | Behandlung des Leberzellkarzinoms         |
| Greek     | N-{2-[(6-{[(2,6-Διχλωρο-3,5-διμεθοξυφαινυλο)καρβαμοϋλο](μεθυλ)αμινο}πυριμιδινο-4-υλ)αμινο]-5-(4-αιθυλοπιπεραζιν-1-υλο)φαινυλ}προπ-2-εναμίδιο          | Θεραπεία του ηπατοκυτταρικού καρκινώματος |

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

| Language   | Active ingredient                                                                                                                            | Indication                               |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Hungarian  | N-{2-[(6-{[(2,6-diklór-3,5-dimetoxifenil)karbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-énamid            | Hepatocelluláris carcinoma kezelése      |
| Italian    | N-{2-[(6-{[(2,6-dicloro-3,5-dimetossifenil)-karbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamide        | Trattamento del carcinoma epatocellulare |
| Latvian    | N-{2-[(6-{[(2,6-dihlor-3,5-dimetoksifenil)karbamoil}(metil)amino}pirimidīn-4-il)amino]-5-(4-etilpiperazīn-1-il)fenil}prop-2-enamīds          | Hepatocellulāras karcinomas ārstēšana    |
| Lithuanian | N-{2-[(6-{[(2,6-dichlor-3,5-dimetoksifenil)karbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamidas        | Hepatoceliulinės karcinomos gydymas      |
| Maltese    | N-{2-[(6-{[(2,6-dikloro-3,5-dimetossifenil)karbamoil}(metil)amino}pirimidin-4-yl)amino]-5-(4-etilpiperazin-1-yl)fenil}prop-2-enamid          | Kura tal-karċinoma epatoċellulari        |
| Polish     | N-{2-[(6-{[(2,6-Dichloro-3,5-dimetoksyfenylo)karbamoiło}(metylo)amino}pyrimidyn-4-ilo)amino]-5-(4-etylopiperazyn-1-ilo)fenylo}prop-2-enoamid | Leczenie raka wątrobowokomórkowego       |
| Portuguese | N-{2-[(6-{[(2,6-dicloro-3,5-dimetoxifenil)carbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamida          | Tratamento do carcinoma hepatocelular    |
| Romanian   | N-{2-[(6-{[(2,6-dicloro-3,5-dimetoxifenil)carbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamidă          | Tratamentul carcinomului hepatocelular   |
| Slovak     | N-{2-[(6-{[(2,6-dichlór-3,5-dimetoxifyfenyl)karbamoyl}(metyl)amino}pyrimidín-4-yl)amino]-5-(4-etylperazín-1-yl)fenyl}prop-2-enamid           | Liečba hepatocelulárneho karcinómu       |
| Slovenian  | N-{2-[(6-{[(2,6-dikloro-3,5-dimetoksifenil)karbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperazin-1-il)fenil}prop-2-enamid          | Zdravljenje hepatocelularnega karcinoma  |
| Spanish    | N-{2-[(6-{[(2,6-dicloro-3,5-dimetoxifenil)carbamoil}(metil)amino}pirimidin-4-il)amino]-5-(4-etilpiperacin-1-il)fenil}prop-2-enamida          | Tratamiento del carcinoma hepatocelular  |
| Swedish    | N-{2-[(6-{[(2,6-diklor-3,5-dimetoxifyfenyl)karbamoyl}(metyl)amino}pyrimidin-4-yl)amino]-5-(4-etylperazazin-1-yl)fenyl}prop-2-enamid          | Behandling av hepatocellulärt karcinom   |
| Norwegian  | N-{2-[(6-{[(2,6-diklor-3,5-dimetoksyfenyl)karbamoyl}(metyl)amino}pyrimidin-4-yl)amino]-5-(4-etylperazazin-1-yl)fenyl}prop-2-enamid           | Behandling av hepatocellulært karsinom   |
| Icelandic  | N-{2-[(6-{[(2,6-díklór-3,5-dímetoxýfenýl)karbamóýl}(metýl)amínó}pýrímídín-4-ýl)amínó]-5-(4-etýlpíperasín-1-ýl)fenýl}próp-2-enamíð            | Meðferð við lifrarfrumukrabbameini       |