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EMA/COMP/698281/2015
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide for treatment of neuroblastoma

On 11 November 2015, orphan designation (EU/3/15/1580) was granted by the European Commission to Pharma Gateway AB, Sweden, for N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide (also known as entrectinib) for the treatment of neuroblastoma.

What is neuroblastoma?

Neuroblastoma is a cancer of certain nerve cells which is usually seen as a lump in the abdomen or around the spine. Symptoms may include weakness, bone pain, loss of appetite and fever.

Neuroblastoma is the most common solid tumour outside the brain in children. In many cases it is present at birth but is diagnosed later when the cancer has spread to other parts of the body and the child begins to show symptoms of the disease.

Neuroblastoma is a long-term debilitating and life-threatening disease that is associated with poor long-term survival.

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

At the time of designation, neuroblastoma affected approximately 1.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 56,000 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, several methods were authorised in the EU for the treatment of neuroblastoma, including surgery, chemotherapy (medicines to treat cancer) and radiotherapy (treatment with radiation).

*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 512,900,000 (Eurostat 2015).



The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with neuroblastoma because early studies in experimental models show that, when given with other chemotherapy medicines, it helps reduce tumour size. In addition, early clinical studies show a response in patients who did not respond to currently available treatments. These assumptions 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 works by blocking the action of certain enzymes known as 'tyrosine kinases', such as TrkA, TrkB, TrkC, ROS1 and ALK. These enzymes are overactive in some cancer cells, including neuroblastoma, and stimulate the growth of cancer cells. By blocking these enzymes, the medicine is expected to stop the cancer cells from dividing, and thereby slowing 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 neuroblastoma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for neuroblastoma. Orphan designation of the medicine had been granted in the United States for neuroblastoma.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 October 2015 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:

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 languages¹, Norwegian and Icelandic

| Language | Active ingredient | Indication |
|-----------|--|-------------------------------|
| English | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide | Treatment of neuroblastoma |
| Bulgarian | N-[5-(3,5-дифлуоробензил)-1H-индазол-3-ил]-4-(4-метилпиперазин-1-ил)-2-(тетраhydro-2H-пиран-4-иламино)бензамид | Лечение на невробластом |
| Croatian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazin-1-il)-2-(tetrahidro-2H-piran-4-ilamino)benzamid | Liječenje neuroblastoma |
| Czech | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamid | Léčba neuroblastomu |
| Danish | N-[5-(3,5-difluorbenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamid | Behandling af neuroblastom |
| Dutch | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide | Behandeling van neuroblastoom |
| Estonian | N-[5-(3,5-difluorobensüül)-1H-indasool-3-üül]-4-(4-metüülpiperasiin-1-üül)-2-(tetrahüdro-2H-püraan-4-üülamino)bensamiid | Neuroblastoomi ravi |
| Finnish | N-[5-(3,5-difluorobentsyyli)-1H-indatsol-3-yyli]-4-(4-metyyli-1-piperatsinyyli)-2-(tetrahydro-2H-pyran-4-yyliamino)-bentsamidi | Neuroblastooman hoito |
| French | N-[5-(3,5-difluorobenzyle)-1H-indazol-3-yl]-4-(4-méthylpipérazine-1-yl)-2-(tétrahydro-2H-pyrane-4-ylamino)benzamide | Traitement du neuroblastome |
| German | N-[5-(3,5-Difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamid | Behandlung des Neuroblastoms |
| Greek | N-[5-(3,5-διφλουοροβενζυλο)-1H-ινδαζολο-3-υλο]-4-(4-μεθυλοπιπεραζινο-1-υλο)-2-(τετραϋδρο-2H-πυρανο-4-υλαμινο)βενζαμιδη | Θεραπεία του νευροβλαστώματος |
| Hungarian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazin-1-il)-2-(tetrahidro-2H-pirán-4-ilamino)benzamid | Neuroblastoma kezelése |
| Italian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazina-1-il)-2-(tetraidro-2H-pirano-4-ilamino)benzammide | Trattamento del neuroblastoma |
| Latvian | N-[5-(3,5-difluorbenzil)-1H-indazol-3-il]-4-(4-metilpiperazīn-1-il)-2-(tetrahidro-2H-pirān-4-ilamino)benzamīds | Neiroblastomas ārstēšana |

¹ At the time of designation

| Language | Active ingredient | Indication |
|------------|--|-------------------------------|
| Lithuanian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazin-1-il)-2-(tetrahidro-2H-piran-4-ilamin)benzamid | Neuroblastomos gydymas |
| Maltese | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide | Kura tan-newroblastoma |
| Polish | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazyno-1-yl)-2-(tetrahydro-2H-piran-4-ylamino)benzamid | Leczenie nerwiaka płodowego |
| Portuguese | N-[5-(3,5-difluorobenzil)-1H-indazole-3-ilo]-4-(4-Metilpiperazina-1-ilo)-2-(tetra-hidro-2H-piran-4-ilamino)benzamida | Tratamento do neuroblastoma |
| Romanian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazină-1-il)-2-(tetrahidro-2H-piran-4-il amino)benzamidă | Tratamentul neuroblastomului |
| Slovak | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazín-1-yl)-2-(tetrahydro-2H-pyrán-4-ylamino)benzamid | Liečba neuroblastómu |
| Slovenian | N-[5-(3,5-difluorobenzil)-1H-indazol-3-il]-4-(4-metilpiperazin-1-il)-2-(tetrahidro-2H-piran-4-ilamino)benzamid | Zdravljenje nevroblastoma |
| Spanish | N-[5-(3,5-difluorobencil)-1H-indazol-3-il]-4-(4-metilpiperazin-1-il)-2-(tetrahidro-2H-piran-4-ilamino)benzamida | Tratamiento del neuroblastoma |
| Swedish | N-[5-(3,5-difluorobensyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamin)bensamid | Behandling av neuroblastom |
| Norwegian | N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamin)benzamid | Behandling av nevroblastom |
| Icelandic | N-[5-(3,5-difluórbensýl)-1H-indasól-3-ýl]-4-(4-methýlpíperasín-1-ýl)-2-(tetrahýdró-2H-pýran-4-ýlamínó)bensamíð | Meðferð við taugakímfrumuæxli |