



10 December 2018
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Public summary of opinion on orphan designation

6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile for the treatment of medullary thyroid carcinoma

On 26 October 2018, orphan designation (EU/3/18/2071) was granted by the European Commission to Loxo Oncology Limited, United Kingdom, for 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (also known as LOXO-292) for the treatment of medullary thyroid carcinoma.

What is medullary thyroid carcinoma?

Medullary thyroid carcinoma is a type of cancer affecting the thyroid, a small gland at the base of the neck that produces thyroid hormones.

The thyroid is composed of two main cell types: follicular cells, which produce hormones that help regulate growth and metabolism (the process of breaking down substances in the body), and parafollicular cells, which produce a hormone called calcitonin that helps to regulate calcium levels in the blood.

Medullary thyroid carcinoma originates from the parafollicular cells, and represents less than 5% of all thyroid cancers. Signs of cancer are difficult to detect in early stages of the disease and are often limited to a single local swelling of the thyroid which is not painful but can be felt by touching. Patients are frequently diagnosed when the disease has spread locally giving symptoms such as shortness of breath, difficulties in swallowing or changes in the voice. Some patients may have severe diarrhoea as a first sign of the disease.

Medullary thyroid carcinoma is a long-term debilitating disease which can be life-threatening if the cancer cannot be removed by surgery or spreads to other parts of the body.

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

At the time of designation, medullary thyroid carcinoma affected less than 0.5 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 26,000 people*, and is below the

*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 517,400,000 (Eurostat 2018).



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, the medicines Cometriq (cabozantinib) and Caprelsa (vandetanib) were authorised for the treatment of medullary thyroid cancer. Surgery was also used to remove the thyroid in some cases.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with medullary thyroid cancer because early data show that patients in whom other treatments had failed responded to treatment with this medicine. 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 acts by blocking the activity of a protein called RET, which normally plays a role in the development of several organs. Many patients with medullary thyroid cancer have mutations (changes) in the gene for RET. These mutations cause RET to be activated in an uncontrolled manner, which in turn makes thyroid parafollicular cells multiply out of control and become cancerous. By blocking the activity of RET, the medicine is expected to 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 medullary thyroid cancer were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for medullary thyroid cancer 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 September 2018 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	6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxy-pyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	Treatment of medullary thyroid carcinoma
Bulgarian	6-(2-хидрокси-2-метилпропокси)-4-(6-(6-((6-метокси-пиридин-3-ил)метил)-3,6-диазабицикло[3.1.1]хептан-3-ил)пиридин-3-ил)пиразоло[1,5-а]пиридин-3-карбонитрил	Лечение на медуларен карцином на щитовидната жлеза
Croatian	6-(2-hidroksi-2-metilpropoksi)-4-(6-(6-((6-metoksipiridin-3-il)metil)-3,6-diazabiklo[3.1.1]heptan-3-il)piridin-3-il)pirazol[1,5-a]piridin-3-karbonitril	Liječenje medularnog raka štitnjače
Czech	6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-metoxypyridin-3-yl)methyl)-3,6-diazabicyklo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-3-karbonitril	Léčba medulárního karcinomu štítné žlázy
Danish	6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxy-pyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-3-carbonitril	Behandling af medullært thyreoideakarcinom
Dutch	6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxy-pyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazool[1,5-a]pyridine-3-carbonitril	Behandeling van medullair schildkliercarcinoom
Estonian	6-(2-hüdroksü-2-metüülpropoksü)-4-(6-(6-((6-metoksü-püridiin-3-üül)metüül)-3,6-diasabitsüklo[3.1.1]heptaan-3-üül)püridiin-3-üül)pürasolo[1,5-a]püridiin-3-karbonitriil	Medullaarse kilpnäärmevähi ravi
Finnish	6-(2-hydroksi-2-metyyli-propoksi)-4-(6-(6-((6-metoksipyridiini-3-yl)metyyli)-3,6-diatsabisyklo[3.1.1]heptaani-3-yl)pyridiini-3-yl)pyratsolo[1,5-a]pyridiini-3-karbonitriili	Medullaarisen kilpirauhaskarsinooman hoito
French	6-(2-hydroxy-2-méthylpropoxy)-4-(6-(6-((6-méthoxy-pyridin-3-yl)méthyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	Traitement du cancer médullaire de la thyroïde
German	6-(2-Hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxy-pyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-3-carbonitril	Behandlung des medullären Schilddrüsenkarzinoms

¹ At the time of designation

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Greek	6-(2-υδροξυ-2-μεθυλοπροποξυ)-4-(6-(6-((6-μεθοξυπυριδιν-3-υλο)μεθυλο)-3,6-διαζαδικυκλο[3.1.1]επταν-3-υλο)πυριδιν-3-υλο)πυραζολο[1,5-α]πυριδινο-3-καρβονιτριλιο	Θεραπεία του μυελοειδούς καρκινώματος του θυρεοειδούς.
Hungarian	6-(2-hidroxi-2-metilpropoxi)-4-(6-(6-((6-metoxipiridin-3-il)metil)-3,6-diazabiciklo[3.1.1]heptan-3-il)piridin-3-il)pirazolo[1,5-a]piridin-3-karbonitril	Medulláris thyroid carcinoma kezelése
Italian	6-(2-idrossi-2-metilpropossi)-4-(6-(6-((6-metossipiridin-3-il)metil)-3,6-diazabiciclo[3.1.1]eptan-3-il)piridin-3-il)pirazolo[1,5-a]piridina-3-carbonitrile	Trattamento del carcinoma midollare della tiroide
Latvian	6-(2-hidroksi-2-metilpropoksi)-4-(6-(6-((6-metoksipiridīn-3-il)metil)-3,6-diazabiciklo[3.1.1]heptān-3-il)piridīn-3-il)pirazolo[1,5-a]piridīn-3-karbonitrils	Medulāras vairogdziedzera karcinomas ārstēšanai
Lithuanian	6-(2-hidroksi-2-metilpropoksi)-4-(6-(6-((6-metoksipiridin-3-il)metil)-3,6-diazabiciklo[3.1.1]heptan-3-il)piridin-3-il)pirazolo[1,5-a]piridino-3-karbonitrilas	Medulinės skydliaukės karcinomos gydymas
Maltese	6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile	Kura tal-karċinoma tal-mudullun tat-tirojje
Polish	6-(2-hydroksy-2-metylopropoksy)-4-(6-(6-((6-metoksypirydyn-3-ylo)metylo)-3,6-diazabicyklo[3.1.1]heptan-3-ylo)pirydyn-3-ylo)pirazolo[1,5-a]pirydyno-3-karbonitryl	Leczenie raka rdzeniastego tarczycy
Portuguese	6-(2-Hidroxi-2-metilpropoxi)-4-(6-(6-((6-metoxipiridin-3-il)metil)-3,6-diazabiciclo[3.1.1]heptan-3-il)piridin-3-il)pirazolo[1,5-a]piridina-3-carbonitrilo	Tratamento do carcinoma medular da tiróide
Romanian	6-(2-hidroxi-2-metilpropoxi)-4-(6-(6-((6-metoxipiridin-3-il)metil)-3,6-diazabiciclo[3.1.1]heptan-3-il)piridin-3-il)pirazolo[1,5-a]piridin-3-carbonitril	Tratamentul carcinomului medular tiroidian
Slovak	6-(2-hydroxy-2-metylpropoxy)-4-(6-(6-((6-metoxypyridín-3-yl)metyl)-3,6-diazabicyklo[3.1.1]heptán-3-yl)pyridín-3-yl)pyrazolo[1,5-a]pyridín-3-karbonitril	Liečba medulárneho karcinómu štítnej žľazy
Slovenian	6-(2-hidroksi-2-metilpropoksi)-4-(6-(6-((6-metoksipiridin-3-il)metil)-3,6-diazabiciklo[3.1.1]heptan-3-il)piridin-3-il)pirazolo[1,5-a]piridin-3-karbonitril	Zdravljenje medularnega karcinoma ščitnice
Spanish	6-(2-hidroxi-2-metilpropoxi)-4-(6-(6-((6-metoxipiridin-3-il)metil)-3,6-diazabiciclo[3.1.1]heptano-3-il)piridin-3-yl)pirazolo[1,5-a]piridina-3-carbonitrilo	Tratamiento del cáncer medular de tiroides
Swedish	6-(2-hydroxi-2-metylpropoxy)-4-(6-(6-((6-metoxipyridin-3-yl)metyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-3-karbonitril	Behandling av medullär thyreoideacancer

Language	Active ingredient	Indication
Norwegian	6-(2-hydroksy-2-metylpropoksy)-4-(6-(6-((6-metoksy-pyridin-3-yl)metyl)-3,6-diazabisyklo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-3-karbonitril	Behandling av medullært thyreoideacarcinom
Icelandic	6-(2-hýdroxý-2-metýlprópoxy)-4-(6-(6-((6-metoxýpýridín-3-ýl)metyl)-3,6-díasabísýkló[3.1.1]heptan-3-ýl)pýridín-3-yl)pýrasóló[1,5-a]pýridín-3-karbónítríl	Meðferð á merggerðarkrabbameini í skjaldkirtli

Withdrawn