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EMA/COMP/844899/2015
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate for the treatment of soft tissue sarcoma

On 11 January 2016, orphan designation (EU/3/15/1606) was granted by the European Commission to TMC Pharma Services Ltd, United Kingdom, for (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate (also known as LOXO-101) for the treatment of soft tissue sarcoma.

What is soft tissue sarcoma?

Soft tissue sarcoma is a type of cancer that affects the soft, supportive tissues of the body. It can occur in muscles, blood vessels, fat tissue or in other tissues that support, surround and protect organs. Patients with soft tissue sarcoma do not usually have symptoms in the early stages of the disease. First symptoms appear when the tumour grows large enough to cause swelling and pain.

Soft tissue sarcoma is a long-term debilitating and life-threatening disease, particularly when the cancer has spread to other parts of the body.

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

At the time of designation, soft tissue sarcoma affected not more than 3 in 10,000 people in the European Union (EU). This was equivalent to a total of not more than 154,000 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, the main treatment for early-stage soft tissue sarcoma was surgery. For large sarcomas, surgery was usually followed by radiotherapy (treatment with radiation) 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 512,900,000 (Eurostat 2015).

chemotherapy (medicines to treat cancer) to kill any cancer cells that were left behind. Several medicines were authorised in the EU for the treatment of soft tissue sarcoma including doxorubicin.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with soft tissue sarcoma because it works in a different way to other treatments and early studies indicate that it might reduce the spread of the cancer in patients with advanced disease. 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 is a 'tyrosine kinase inhibitor', which means that it works by blocking enzymes known as tyrosine kinases. These enzymes can be found in some receptors in cancer cells, including the tropomyosin receptor kinase (TRK) family. TRK receptors are involved in stimulating the cells to divide uncontrollably. By blocking these receptors, the medicine is expected to stop cell division and lead to cell death. This is expected to slow down the growth and spread of soft tissue sarcoma.

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 soft tissue sarcoma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for soft tissue sarcoma. Orphan designation of the medicine had been granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 December 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	(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate	Treatment of soft tissue sarcoma
Bulgarian	(S)-N-(5-((R)-2-(2,5-дифлуорофенил)пиролидин-1-ил)пиразоло[1,5-а]пиримидин-3-ил)-3-хидроксипиролидин-1-карбоксамид хидросулфат	Лечение на сарком на меките тъкани
Croatian	(S)-N-(5-((R)-2-(2,5-difluorofenil)pirolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-hidroksipirolidin-1-karboksamid hidrogensulfat	Liječenje sarkoma mekih tkiva
Czech	(S)-N-(5-((R)-2-(2,5-difluorofenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrolidin-1-karboxamidu hydrogensíran	Léčba sarkomu měkkých tkání
Danish	(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidin-1-carboxamidhydrogensulfat	Behandling af bløddelssarkom
Dutch	(S)-N-(5-((R)-2-(2,5-difluorfenyl)pyrrolidine-1-yl)pyrazolo[1,5-a]pyrimidine-3-yl)-3-hydroxypyrrolidine-1-carboxamidewaterstofsulfaat	Behandeling weke delen sarcoom
Estonian	(S)-N-(5-((R)-2-(2,5-difluorofenüül)pürrolidiin-1-yl)püratsool[1,5-a]pyrimidin-3-yl)-3-hüdroksüpürrolidiin-1-karboksamiid vesiniksulfaat	Pehmele kudede sarkoomi ravi
Finnish	(S)-N-(5-((R)-2-(2,5-difluorofenyyl)pyrrolidiini-1-yyli)pyratsolo[1,5-a]pyrimidiini-3-yyli)-3-hydroksipyrrolidiini-1-karboksamidivetysulfaatti	Pehmytkudossarkooman hoito
French	(S)-N-(5-((R)-2-(2,5-difluorophényl)pyrrolidine-1-yl)pyrazolo[1,5-a]pyrimidine-3-yl)-3-hydroxypyrrolidine-1-carboxamide- hydrogène-sulfate	Traitement des sarcomes des tissus mous
German	(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidin-1-carboxamid-hydrogensulfat	Behandlung des Weichteilsarkoms
Greek	όξινη θειική (S)-N-(5-((R)-2-(2,5-διφθοροφαινυλ)πυρρολιδιν-1-υλ)πυραζολο[1,5-α]πυριμιδιν-3-υλ)-3-υδροξυπυρολιδινο-1-καρβοξαμίδη	Θεραπεία του σαρκόματος των μαλακών ιστών
Hungarian	(S)-N-(5-((R)-2-(2,5-difluorofenil)pirrolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-hidroxipirrolidin-1-karboxamid-hidrogénsulfát	Lágy szöveti sarcoma kezelése
Italian	(S)-N-(5-((R)-2-(2,5-difluorofenil)pirrolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-idrossipirrolidina-1-carbossamide idrogeno solfato	Trattamento dei sarcomi dei tessuti molli
Latvian	(S)-N-(5-((R)-2-(2,5-difluorfenil)pirolidīn-1-il)pirazol[1,5-a]pirimidīn-3-il)-3-hidroksipirolidīn-1-karboksamīda ūdeņraža sulfāts	Mīksto audu sarkomas ārstēšana

¹ At the time of designation

Language	Active ingredient	Indication
Lithuanian	(S)-N-(5-((R)-2-(2,5-difluorofenil)pirolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-hidroksipirolidino-1-karboksamido vandenilio sulfatas	Minkštųjų audinių sarkomos gydymas
Maltese	(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate	Kura tas-sarkoma tat-tessuti rotob
Polish	Wodorosiarczan (S)-N-(5-((R)-2-(2,5-difluorofenyl)pirolidyno-1-ylo)pirazolo[1,5-a]pirymidyno-3-ylo)-3-hydroksypirolidyno-1-karboksamidu	Leczenie mięsaków tkanek miękkich
Portuguese	Hidrogenossulfato de (S)-N-(5-((R)-2-(2,5-difluorofenil)pirrolidin-1-il)pirazol[1,5-a]pirimidin-3-il)-3-hidroxipirrolidina-1-carboxamida	Tratamento do sarcoma dos tecidos moles
Romanian	Hidrogen sulfat de (S)-N-(5-((R)-2-(2,5-difluorofenil)pirolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-hidroxipirolidină-1-carboxamidă	Tratamentul sarcomului țesuturilor moi
Slovak	(S)-N-(5-((R)-2-(2,5-difluórofenyl)pyrolidín-1-yl)pyrazolo[1,5-a]pyrimidín-3-yl)-3-hydroxypyrolidín-1-karboxamid hydrogensulfát	Liečba sarkómu mäkkých tkanív
Slovenian	(S)-N-(5-((R)-2-(2,5-difluorofenil)pirolidin-1-il)pirazolo[1,5-a]pirimidin-3-il)-3-hidroksipirolidin-1-karboksamid hidrogensulfat	Zdravljenje sarkoma mehkih tkiv
Spanish	Sulfato de hidrógeno (S)-N-(5-((R)-2-(2,5-difluorofenilo)pirrolidina-1-yl)pirazolo[1,5-a]pirimidina-3-yl)-3-hidroxipirrolidina-1-carboxamida	Tratamiento del sarcoma de tejidos blandos
Swedish	(S)-N-(5-((R)-2-(2,5-Difluorfenyl)pyrrolidin-1-yl)pyrazol[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidin-1-karboxamidvätesulfat	Behandling av mjukdelssarkom
Norwegian	(S)-N-(5-((R)-2-(2,5- difluorfenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroksypyrrolidin-1-karboksamid hydrogensulfat	Behandling av bløtvevssarkom
Icelandic	(S)-N-(5-((R)-2-(2,5-díflúorfenýl)pýrrólídín-1-ýl)pýrasóló[1,5-a]pýrimídín-3-ýl)-3-hýdroxýpýrrólídín-1-karboxamíðvetnissúlfat	Meðferð við mjúkvæfjasarkmeini