

3 May 2017  
EMA/142686/2017  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

(S)-ethyl 2-amino-3-(4-(2-amino-6(-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate for the treatment of carcinoid syndrome

On 30 May 2016, orphan designation (EU/3/09/661) was granted by the European Commission to Ipsen Pharma, France, for (S)-ethyl 2-amino-3-(4-(2-amino-6(-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate (also known as telotristat etiprate) for the treatment of carcinoid syndrome.

### What is carcinoid syndrome?

Carcinoid syndrome is a condition that may develop in patients with a type of cancer called a neuroendocrine or carcinoid tumour when the tumour spreads to the liver.

Carcinoid tumours are slow-growing tumours that develop in hormone producing cells usually in the appendix or in the small bowel. The tumour can secrete hormones such as serotonin but these are normally broken down by the liver and do not cause symptoms. However, when the tumour spreads to the liver, the hormones can enter the blood stream and cause symptoms of carcinoid syndrome such as severe diarrhoea, belly cramps and flushing (reddening of the skin). Some patients also develop valvular heart disease (damage to the valves of the heart) or constriction of the airway (bronchoconstriction).

Carcinoid syndrome is a debilitating and life-threatening condition because it can lead to heart failure and difficulty breathing.

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

At the time of designation, carcinoid syndrome affected approximately 0.7 in 10,000 people in the European Union (EU). This was equivalent to a total of around 36,000 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).

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\*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 2016).

## What treatments are available?

At the time of designation, somatostatin analogues, such as octreotide and lanreotide, were authorised in the EU to treat the symptoms caused by carcinoid tumours. Other medicines used to treat the condition included everolimus, sunitinib, and interferon alfa. Patients with carcinoid tumours could be cured using surgery to remove the tumours if they are found early.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with carcinoid syndrome because initial studies in patients whose condition has not responded to standard treatments, or who cannot be given them, showed that their symptoms improved. 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 expected to work by blocking an enzyme known as tryptophan hydroxylase (TPH), which is responsible for the production of the hormone serotonin. Serotonin is one of the hormones that are produced in large amounts in patients with carcinoid syndrome. By blocking TPH, the medicine is expected to stop the production of serotonin, reducing the symptoms of the condition.

## 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 carcinoid syndrome were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for carcinoid syndrome.

This medicine had been designated orphan on 8 October 2009 for the treatment of carcinoid tumours. The original designation was granted to Lexicon Celtic Ltd, United Kingdom; sponsorship was transferred to Ipsen Pharma, France, in April 2015. At the request of the sponsor and having assessed the additional data submitted, the COMP adopted an opinion on 21 April 2016 recommending the change of the orphan condition from carcinoid tumour to carcinoid syndrome.

Orphan designation of the medicine has been granted in the United States for managing symptoms of carcinoid syndrome associated with carcinoid tumour.

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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	(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate	Treatment of carcinoid syndrome
Bulgarian	(S)-етил 2-амино-3-(4-(2-амино-6-((R)-1-(4-хлоро-2-(3-метил-1H-пиразол-1-ил)фенил)-2,2,2-трифлуороетокси)пиримидин-4-ил)фенил)пропаноат	Лечение на карциноиден синдром
Croatian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoksi)pirimidin-4-il)fenil)propanoat	Liječenje karcinoidnog sindroma
Czech	(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chlor-2-(3-methyl-1H-pyrazol-1-yl)fenyl)-2,2,2-trifluorethoxy)pyrimidin-4-yl)fenyl)propanoát	Léčba karcinoidního syndromu
Danish	(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoat	Behandling af carcinoid syndrom
Dutch	(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloor-2-(3-methyl-1H-pyrazol-1-yl)fenyl)-2,2,2-trifluorethoxy)pyrimidine-4-yl)fenyl)propanoaat	Behandeling van carcinoïdsyndroom
Estonian	(S)-etüül 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metüül-1H-pürasool-1-üül)fenüül)-2,2,2-trifluoroetoksü)pürimidiin-4-üül)fenüül)propanoaat	Kartsinoidsündroomi ravi
Finnish	(S)-etyyli 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metyyli-1H-pyratsoli-1-yyli)fenyyli)-2,2,2-trifluoroetoksi)pyrimidiini-4-yyli)fenyyli)propanoatti	Karsinoidisyndrooman hoito
French	propanoate de (S)-éthyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-méthyl-1H-pyrazol-1-yl)phényl)-2,2,2-trifluoroéthoxy)pyrimidine-4-yl)phényl)	Traitement du syndrome carcinoïde
German	(S)-Ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chlor-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluorethoxy)pyrimidin-4-yl)phenyl)propanoat	Behandlung von Karzinoidsyndrom
Greek	(S)-αιθυλ 2-αμινο-3-(4-(2-αμινο-6-((R)-1-(4-χλωρο-2-(3-μεθυλ-1H-πυραζολ-1-υλο)φαινυλο)-2,2,2-τριφθοροεθοξυ) πυριμιδιν-4-υλο)φαινυλο)προπανοϊκό	Θεραπεία του καρκινοειδούς συνδρόμου
Hungarian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoksi)pirimidin-4-il)fenil)propanoát	Karcinoid szindróma kezelése
Italian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-cloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetossi)pirimidin-4-il)fenil)propanoato	Trattamento della sindrome da carcinoide
Latvian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-hloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoksi)pirimidīna-4-il)fenil)propanoāts	Karcinoīdā sindroma ārstēšana

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

Language	Active ingredient	Indication
Lithuanian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoksi)pirimidin-4-il)fenil)propanoatas	Karcinoido sindromo gydymas
Maltese	(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate	Kura tas-sindrome karċinojde
Polish	propionian (S)-etylo 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-metylo-1H-pirazolo-1-ylo)fenylo)-2,2,2-trifluoroetoksy)pirymidyno-4-ylo)fenylu	Leczenie zespołu rakowiaka
Portuguese	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-cloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoxi)pirimidin-4-il)fenil)propanoato	Tratamento da síndrome carcinoide
Romanian	propanoat de (S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-clor-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoxi)pirimidină-4-il)fenil)	Tratamentul sindromului carcinoïd
Slovak	(S)-etyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-metyl-1H-pyrazol-1-yl)fenyl)-2,2,2-trifluoroetoxi)pyrimidín-4-yl)fenyl)propanoát	Liečba karcinoidného syndrómu
Slovenian	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoksi)pirimidin-4-il)fenil)propanoat	Zdravljenje karcinoidnega sindroma
Spanish	(S)-etil 2-amino-3-(4-(2-amino-6-((R)-1-(4-cloro-2-(3-metil-1H-pirazol-1-il)fenil)-2,2,2-trifluoroetoxi)pirimidin-4-il)fenil)propanoato	Tratamiento del síndrome carcinoide
Swedish	(S)-etyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-kloro-2-(3-metyl-1H-pyrazol-1-yl)fenyl)-2,2,2-trifluoroetoxi)pyrimidin-4-yl)fenyl)propanoat	Behandling av karcinoidsyndrom
Norwegian	(S)-etyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-klor-2-(3-metyl-1H-pyrazol-1-yl)fenyl)-2,2,2-trifluoretoksy)pyrimidin-4-yl)fenyl)propanoat	Behandling av karsinoid syndrom
Icelandic	(S)-etýl 2-amínó-3-(4-(2-amínó-6-((R)-1-(4-klór-2-(3-metýl-1H-pýrazól-1-ýl)fenýl)-2,2,2-príflúoretoxý)þýrimidín-4-ýl)fenýl)própanóat	Meðferð carcinoïd heilkennis