



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF

R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea for the treatment of gastric carcinoid

On 14 June 2007, orphan designation (EU/3/07/452) was granted by the European Commission to Trio Medicines Ltd, United Kingdom, for R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea for the treatment of gastric carcinoid.

What is gastric carcinoid?

Gastric carcinoids are tumours that either arise from a specific type of cells in the stomach, called “neuroendocrine” or “enterochromaffin-like” cells, or that demonstrate similar characteristics to these cells. There are three types of gastric carcinoid, and the first two (type I and type II, representing 85% of more of all gastric carcinoids) are thought to be caused or worsened by the high levels of a gastrointestinal hormone, called gastrin, which are observed in these two subtypes. Gastrin is a substance, secreted by other cells in the stomach and the gastrointestinal tract, which stimulates the growth of the neuroendocrine cells, and indirectly stimulates acid production of acid by the stomach. Only a small percentage (less than 5%) of all carcinoids are gastric in origin.

Gastric carcinoids, especially type I and II, are not as malignant as other tumours of the gastrointestinal tract, but can give metastases (repetitive tumours in other parts of the body) and be life-threatening in a percentage of cases.

In some but not all cases, carcinoids can cause a specific set of symptoms, called “carcinoid syndrome”.

What are the methods of treatment available?

Surgical removal of the carcinoid is usually performed, either through an endoscope (gastroscope) or with a classical surgical approach (abdominal incision).

Products derived from somatostatin (a hormone that blocks the secretion of most endocrine or neuroendocrine cells) such as octreotide and lanreotide were authorised for the treatment of carcinoid syndrome, and interferon-alfa was authorised for the treatment of lymphatic or liver metastases from carcinoid tumours, at the time of the application. However, none of these drugs was specifically authorised for non-metastatic carcinoid tumours that do not induce the carcinoid syndrome.

R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea might be of potential significant benefit, because it could be used to treat the carcinoid itself, rather than the metastases or the carcinoid syndrome (which is not always present); also, it can be administered orally, while the existing authorised drugs are given by injection. Finally, the drug could be used in patients who are not candidates for surgery or who refuse it, and to prevent further spread of the disease in advanced cases.

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

According to the information provided by the sponsor, gastric carcinoid was considered to affect less than 46,000 persons in the European Union.

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How is this medicinal product expected to act?

R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea blocks the action of gastrin, by interacting with a specific protein (called gastrin receptor), which is necessary for gastrin to exert its effect. Since gastrin can stimulate the growth of gastric cells, blocking its action is expected to inhibit tumour growth.

What is the stage of development of this medicinal product?

The effects of the medicinal product were evaluated in experimental models in animals.

At the time of submission of the application for orphan designation, no clinical trials in patients with gastric carcinoid were initiated.

R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea was not authorised anywhere worldwide for the treatment of gastric carcinoid, nor designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 12 April 2007 a positive opinion recommending the granting of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which were considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

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*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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**Translations of the active ingredient and indication in all EU languages
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea	Treatment of gastric carcinoid
Bulgarian	R-1-[2,3-дихидро-2-оксо-1-пивалоилметил-5-(2-пиридил)-1 H -1,4-бензодиазепин-3-ил]-3-(3-метиламинофенил)уреа	Лечение на стомашен карциноиден тумор
Czech	R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminofenyl)močovina	Léčba žaludečních karcinoidů
Danish	R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea	Behandling af karcinoid tumor i ventriklen
Dutch	R-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminofenyl)ureum	Behandeling van maagcarcinoïds
Estonian	R-1-[2,3-dihüdro-2-okso-1-pivaloüülmetüül-5-(2-püridüül)-1 H -1,4-bensodiasepiin-3-yl]-3-(3-metüülaminofenüül)uurea	Maokartsinoidi ravi
Finnish	R-1-[2,3-dihydro-2-okso-1-pivaloyylimetyyli-5-(2-pyridyyli)-1 H -1,4-bentsodiatsepiini-3-yl]-3-(3-metyyliaminofenyyli)urea	Mahakarsinoidin hoito
French	R-1-[2,3-dihydro-2-oxo-1-pivaloylméthyl-5-(2-pyridyl)-1 H -1,4-benzodiazépine-3-yl]-3-(3-méthylaminophényl) urée	Traitement des carcinoïdes gastriques
German	R-1-[2,3-Dihydro-2-oxo-1-pivaloyl-methyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea	Behandlung von Magenkarzinoiden
Greek	R-1-[2,3-διϋδρο-2-οξο-1-πιβαλοϋλομεθυλο-5-(2-πυριδυλο)-1 H -1,4-βενζοδιαζεπινο-3-υλο]-3-(3-μεθυλαμινοφαινυλ)ουρία	Θεραπεία των γαστρικών καρκινοειδών
Hungarian	R-1-[2,3-dihidro-2-oxo-1-pivaloilmetil-5-(2-piridil)-1 H -1,4-benzodiazepin-3-il]-3-(3-metilaminofenil)urea	Gyomor karcinoid kezelése
Italian	R-1-[2,3-diidro-2-oxo-1-pivaloil metil-5-	Trattamento del carcinoide gastrico

	(2-piridil)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metilaminofenil)urea	
Latvian	R-1-[2,3-dihidro-2-okso-1-pivaloimetil-5-(2-piridil)-1 H -1,4-benzodiazepīna-3-il]-3-(3-metilaminofenil)urīnviela	Kuņģa karcinoīda ārstēšana
Lithuanian	R-1-[2,3-dihidro-2-okso-1-pivaloilmetil-5-(2-piridil)-1 H -1,4-benzodiazepin-3-il]-3-(3-metilaminofenil)urėja	Skrandžio karcinoidų gydymas
Maltese	(R)-1-[2,3-dihydro-2-oxo-1-pivaloylmethyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea	Kura tal-karċinojdi gastiċi
Polish	R-1-[2,3-dihydro-2-okso-1-pivaloylmetyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metyloaminofenyl)mocznik	Leczenie rakowiaka żołądka
Portuguese	R-1-[2,3-dihydro-2-oxo-1-pivaloil-metil-5-(2-piridil)-1 H -1,4-benzodiazepina-3-yl]-3-(3-metilaminofenil)ureia	Tratamento dos carcinóides gástricos
Romanian	R-1-[2,3-dihidro-2-oxo-1-pivaloilmetil-5-(2-piridil)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metil-aminofenil)uree	Tratamentul carcinoidului gastric
Slovak	R-1-[2,3-dihydro-2-oxo-1-pivaloylmetyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metylaminofenyl)močovina	Liečba žalúdočného karcinoidu
Slovenian	R-1-[2,3-dihidro-2-okso-1-pivaloil metil-5-(2-piridil)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metillaminofenil) sečnina	Zdravljenje karcinoma želodca
Spanish	R-1-[2,3-dihidro-2-oxo-1-pivaloilmetil-5-(2-piridil)-1 H -1,4-benzodiazepín-3-yl]-3-(3-metil aminofenil)urea	Tratamiento del tumor carcinoide gástrico
Swedish	R-1-[2,3-dihydro-2-oxo-1-pivaloylmetyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metyl aminofenyl) urea	Behandling av magcarcinoid
Norwegian	R-1-[2,3-dihydro-2-okso-1-pivaloylmetyl-5-(2-pyridyl)-1 H -1,4-benzodiazepin-3-yl]-3-(3-metylaminofenyl)urea	Behandling av ventrikkelskarsinoid
Icelandic	R-1-[2,3-tvíhýdró-2-oxó-1-pivalóymethýl-5-(2-pýridýl)-1 H -1,4-benzódíazepín-3-ýl]-3-(3-methýlaminóphenýl)þvagefni	Meðhöndlun á magakrabbalíki