



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea for the treatment of gastro-entero-pancreatic neuroendocrine tumours

On 14 December 2015, orphan designation (EU/3/15/1588) was granted by the European Commission to Trio Medicines Ltd, United Kingdom, for (R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea (also known as TR2-A) for the treatment of gastro-entero-pancreatic neuroendocrine tumours.

What are gastro-entero-pancreatic neuroendocrine tumours?

Gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) are tumours that arise from neuroendocrine cells in the gut. These cells release hormones that control various functions of the digestive system. The symptoms of GEP-NETs depend on where in the gut the tumour is growing and on whether it produces excess hormones. Often by the time of diagnosis the tumours have spread to other organs such as the liver.

GEP-NETs are debilitating as they often produce excess hormones that may cause severe symptoms. They are life-threatening if they spread to other organs in the body.

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

At the time of designation, GEP-NETs affected approximately 3.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 180,000 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).

*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).



What treatments are available?

At the time of the application for orphan designation, several products were authorised in the EU for treating GEP-NETs, including octreotide and lanreotide for the management of symptoms, everolimus, and sunitinib.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with GEP-NETs because data from patients treated with the medicine showed reduction of tumour size and in the spread of the tumour to other parts of the body. 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 stops gastrin from interacting with its receptor by blocking the receptor. Gastrin is a hormone that controls the release of acid into the stomach and organises and maintains the normal structure of the stomach lining. Excessive gastrin is thought to stimulate the growth of GEP-NETs. The medicine is expected to stop this growth by blocking the effect of gastrin.

What is the stage of development of this medicine?

The effects of (R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea 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 GEP-NETs were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for GEP-NETs 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 12 November 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	(R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea	Treatment of gastro-entero-pancreatic neuroendocrine tumours
Bulgarian	(R)-1-[1-(4-ацетокси-3,3-диметил-2-оксо-бутил)-2-оксо-5-(пиридин-2-ил)-2,3-дихидро-1H-бензо[е][1,4]дiazепин-3-ил]-3-(3-метиламино-фенил)-уреа	Лечение на гастро-ентеро-панкреатични невроендокринни тумори
Croatian	(R)-1-[1-(4-acetoksi-3,3-dimetil-2-okso-butil)-2-okso-5-(piridin-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilaminofenil)-urea	Liječenje gastroenteropankreatičnih neuroendokrinih tumora
Czech	(R)-1-[1-(4-Acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-fenyl)-urea	Léčba gastro-entero- pankreatických neuroendokrinních tumorů
Danish	(R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea	Behandling af gastro-entero-pancreatiske neuroendocrine tumorer
Dutch	(R)-1-[1-(4-Acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-fenyl)-ureum	Behandeling van gastro-entero-pancreatische neuroendocriene tumoren
Estonian	(R)-1-[1-(4-atsetoksü-3,3-dimetüül-2-oksobutüül)-2-okso-5-(püridiin-2-üül)-2,3-dihüdro-1H-benso[e][1,4]diasepiin-3-üül]-3-(3-metüülaminofenüül)uurea	Gastroenteropankreaatiliste neuroendokriintuumorite ravi
Finnish	(R)-1-[1-(4-asetoksi-3,3-dimetyyli-2-okso-butyyli)-2-okso-5-(pyridiini-2-yyli)-2,3-dihydro-1H-bentso[e][1,4]diatsepiini-3-yyli]-3-(3-metyyliamino-fenyyli)-urea	Maha-suolikanavan ja haiman neuroendokriinisten kasvainten hoito
French	(R)-1-[1-(4-Acétoxy-3,3-diméthyl-2-oxo-butyle)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-méthylamino-phényle)-urée	Traitement des tumeurs neuroendocrines gastroentéropancréatiques
German	(R)-1-[1-(4-Acetoxy-3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-(Pyridin-2-yl)-2,3-Dihydro-1H-Benzo[e][1,4]Diazepin-3-yl]-3-(3-Methylamino-phenyl)-urea	Behandlung von gastro-entero-pankreatischen neuroendokrinen Tumoren

¹ At the time of designation

Language	Active ingredient	Indication
Greek	(R)-1-[1-(4-ακετοξυ-3,3-διμεθυλ-2-οξο-βουτυλ)-2-οξο-5-(πυριδιν-2-υλ)-2,3-διυδρο-1H-βενζο[e][1,4]διαζεπιν-3-υλ]-3-(3-μεθυλαμινο-φαινυλο)-ουρία	Θεραπεία των γαστρεντεροπαγκρεατικών νευροενδοκρινικών όγκων
Hungarian	(R)-1-[1-(4-acetoxi-3,3-dimetil-2-oxo-butil)-2-oxo-5-(piridin-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilamino-fenil)-karbamid	Gasztro-entero-pankreatikus neuroendokrin tumorok kezelése
Italian	(R)-1-[1-(4-metossi-3,3-dimetil-2-oxo-butile)-2-oxo-5-(piridin-2-ile)-2,3-diidro-1H-benzo[e][1,4]diazepin-3-ile]-3-(3-metilammino-fenil)-urea	Trattamento dei tumori gastro-entero-pancreatici neuroendocrini
Latvian	(R)-1-[1-(4-acetoksi-3,3-dimetil-2-okso-butil)-2-okso-5-(piridīn-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepīn-3-il]-3-(3-metilamino-fenil) urīnviela	Kuņģa-zarnu -aizkuņģa dziedzerā neiroendokrīnu audzēju ārstēšana
Lithuanian	(R)-1-[1-(4-acetoksi-3,3-dimetil-2-okso-butil)-2-okso-5-(piridin-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilamino-fenil)-urėja	Neuroendokrininių skrandžio-žarnyno kasos tumorų gydymas
Maltese	(R)-1-[1-(4-acetoxi-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea	Kura ta' tumuri newroendokrini gastro-entero-pankrejatiċi
Polish	(R)-1-[1-(4-Acetoksy-3,3-dimetyl-2-okso-butyl)-2-okso-5-(pirydyn-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-metylamino-fenyl)-mocznik	Leczenie guzów neuroendokrynnych przewodu pokarmowego i trzustki
Portuguese	(R)-1-[1-(4-acetoxi-3,3-dimetil-2-oxo-butil)-2-oxo-5-(piridin-2-il)-2,3-di-hidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilaminofenil)ureia	Tratamento dos tumores neuroendócrinos gastro-entero-pancreáticos
Romanian	(R)-1-[1-(4-acetoxi-3,3-dimetil-2-oxo-butil)-2-oxo-5-(piridin-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilamino-fenil)-uree	Tratamentul tumorilor neuroendocrine gastro-entero-pancreatice
Slovak	(R)-1-[1-(4-Acetoxi-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea	Liečba gastroenteropankreatických neuroendokrinných nádorov
Slovenian	(R)-1-[1-(4-acetoksi-3,3-dimetil-2-okso-butil)-2-okso-5-(piridin-2-yl)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilamin-fenil)-sečnina	Zdravljenje gastro-entero-pankreaticčnih neuroendokrinih tumorjev

Language	Active ingredient	Indication
Spanish	(R)-1-[1-(4-Acetoxi-3,3-dimetil-2-oxo-butil)-2-oxo-5-(piridin-2-il)-2,3-dihidro-1H-benzo[e][1,4]diazepin-3-il]-3-(3-metilamino-fenil)-urea	Tratamiento de los tumores neuroendocrinos gastroenteropancreáticos
Swedish	(R)-1-[1-(4-Acetoxi-3,3-dimetyl-2-oxobutyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-metylamino-fenyl)-urea	Behandling av gastroenteropankreatiska neuroendokrina tumörer
Norwegian	(R)-1-[1-(4-Acetoksi-3,3-dimetyl-2-oksobutyl)-2-okso-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-metylamino-fenyl)-urea	Behandling av gastroenteropankreatiske nevroendokrine tumorer
Icelandic	(R)-1-[1-(4-Asetoxý-3,3-dímethýl-2-oxó-bútýl)-2-oxó-5-(pýridín-2-ýl)-2,3-tvívetnis-1H-bensó[e][1,4]díasepín-3-ýl]-3-(3-metýlamínó-fenýl)-þvagefni	Greining á maga-þarma-bris æxlum af taugainnkirtlatoga