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Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in July 2008 on request of the Sponsor.

Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of

(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate for the treatment of malignant gastrointestinal stromal tumours

On 10 March 2005, orphan designation (EU/3/05/267) was granted by the European Commission to Pfizer Limited, United Kingdom, for (Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate for the treatment of malignant gastrointestinal stromal tumours.

What are malignant gastrointestinal stromal tumours?

Malignant gastrointestinal stromal tumours (GIST) are the most common subtype of gastro-intestinal sarcomas, which belong to the group of soft tissue sarcomas. Soft tissue sarcomas are cancers of the tissues that support, surround and protect the organs of the body, such as muscle tissue and fat tissue. The cause of gastrointestinal stromal tumours is largely unknown. Gastrointestinal stromal tumours are most common in the stomach (60-70%), followed by small intestine (20-30%), and colon and rectum (5%). Gastrointestinal stromal tumours occur predominantly in middle-aged and older persons and are considered as a life-threatening condition.

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

At the time of designation, GIST affected approximately 0.3 in 10,000 people in the European Union (EU)*. This is equivalent to a total of around 14,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

The current methods of treatment are surgical removal of the tumour and treatment with a medicinal product, which belongs to the same group of substances called tyrosine kinase inhibitors, aimed at slowing down and potentially stop the tumor growth.

(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate could be of potential significant benefit for the treatment of malignant GIST, mainly because it could act in a different way and thereby might improve the long-term outcome of the patients. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

*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 25), Norway, Iceland and Liechtenstein. This represents a population of 459,700,000 (Eurostat 2004).

How is this medicine expected to work?

Enzymes are proteins produced by the human body that speed up the conversion of certain substances into other substances. Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate blocks (inhibits) the enzyme tyrosine kinase. This enzyme plays a role in a cascade of molecular reactions to bring a certain signal from outside the cell into the cell thereby controlling the growth of the cells. In cancer cells, the function of this enzyme is disturbed causing uncontrolled growth and multiplication of the cancer cells.

Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate might, by inhibition of this enzyme activity at a certain level in the cascade, help in slowing down or stopping the further growth of the cancer cells.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials in patients with renal cell carcinoma were ongoing.

The medicinal product was not authorised anywhere worldwide for renal cell carcinoma or 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 3 February 2005 a positive opinion recommending the grant of the above-mentioned designation.

Update: (Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate (Sutent) is authorised in the European Union as of 19 July 2006 for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Efficacy is based on time to tumour progression and an increase in survival.

For more information please see www.emea.europa.eu

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 Community) 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.

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

Language	Active Ingredient	Indication
English	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate	Treatment of malignant gastro intestinal stromal tumours
Czech	(Z)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidén)methyl]-2,4-dimethyl-1H-pyrol-3-carboxamid-(S)-2-hydroxysukcinát	Léčba gastrointestinálních stromálních tumorů
Danish	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrol-3-carboxamid (S)-2-hydroxysuccinat	Behandling af malign gastrointestinal stromal tumor
Dutch	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylideen)methyl]-2,4-dimethyl-1H-pyrrol-3-carboxamide (S)-2-hydroxysuccinaat	Behandeling van kwaadaardige gastro-intestinale stromale tumoren
Estonian	(Z)-N-[2-(Dietüülamino)etüül]-5-[(5-fluoro-2-okso-1,2-dihüdro-3Hindool-3-ülideen)metüül]-2,4-dimetüül-1H-pürrool-3-karboksamiid (S)-2-hüdroksüsuksinaat	Pahaloomuliste seedetrakti stroomaalsete kasvajate ravi
Finnish	(Z)-N-[2-(dietyyliamino) etyyli]-5-[(5-fluoro-2-okso-1,2-dihydro-3Hindoli-3-ylideeni)metyyli]-2,4-dimetyyli-1H-pyroli-3-karboksamidi (S)-2-hydroksiysuksinaatti	Ruuansulatuskanavan pahanlaatuisten stroomatuumorien hoito
French	(Z)-N-[2-(Diéthylamino)éthyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidène)méthyl]-2,4-diméthyl-1H-pyrrole-3-carboxamide(S)-2-hydroxysuccinate	Traitement des tumeurs malignes stromales gastrointestinales
German	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-yliden)methyl]-2,4-dimethyl-1H-pyrrol-3-carboxamid (S)-2-hydroxysuccinat	Behandlung von bösartigen gastrointestinalen Stromatumoren
Greek	(Z)-N-[2-(Διαethylαμινο)αιθυλο]-5-[(5-φθορο-2-οξο-1,2-διϋδρο-3H-ινδολο-3-υλιδεν)μεθυλο]-2,4-διμεθυλο-1H-πυρρολο-3-καρβοξαμίδιο (S)-2-υδροξυηλεκτρικό	Θεραπευτική αγωγή των κακοήθων γαστρεντερικών στρωματικών όγκων
Hungarian	(Z)-N-[2-(diethyl-amino)etil]-5-[(5-fluoro-2-oxo-1,2-dihidro-3H-indol-3-ilidén)metil]-2,4-dimetil-1H-pirrol-3-karboxamid (S)-2-hidroxisukcinát	Roszzindulatú gasztrointesztinális stromalis tumorok kezelése
Italian	(Z)- N-2-[(Dietilamino)etil]-5- [(5-fluoro-2-osso-1,2-diidro-3H-indol-3-ilidene)metil]-2,4-dimetil-1H-pirrol-3-carbossiammide (S)-2-idrossisuccinato	Trattamento dei tumori stromali gastrointestinali maligni

Latvian	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate	Ļaundabīga kuņģa-zarnu trakta stromas audzēju terapija
Lithuanian	(Z)-N-[2-(diethylamino)etil]-5-[(5-fluoro-2-okso-1,2-dihidro-3H-indol-3-ylideno)metil]-2,4-dimetil-1H-pirol-3-kraboksamido (S)-2-hidroksisukcinatas	Skrandžio ir žarnyno stromos piktybinių auglių gydymas
Polish	(S)-2- hydroksybursztynian (Z)-N-[2-dietyloamino)etyl]-5-[(5-fluoro-2-oxy-1,2-dihydro-3H-indolo-3-ylidene)metylo]-2,4-dimetylo-1H-pirol-3-karboksyamidu	Leczenie złośliwych nowotworów podścieliska przewodu pokarmowego
Portuguese	(Z)-N-[2-(Dietilamino)etil]-5-[(5-fluoro-2-oxo-1,2-dihidro-3H-indol-3-ilideno)metil]-2,4-dimetil-1H-pirrol-3-carboxamida (S)-2-hidroxisuccinato	Tratamento de tumores estromais gastrintestinais malignos
Slovak	(Z)-N-[2-(dietylamin)etyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidén)metyl]-2,4-dimetyl-1H-pyrol-3-karboxamid-(S)-2-hydroxysukcinát	Liečba malígnych gastrointestinálnych stromatóznych nádorov
Slovenian	(Z)-N-[2-(diethylamino)etil]-5-[(5-fluoro-2-okso-1,2-dihidro-3H-indol-3-iliden)metil]-2,4-dimetil-1H-pirol-3-karboksamid (S)-2-hidroksisukcinat	Zdravljenje malignih gastrointestinalnih stromalnih tumorjev
Spanish	(Z)-N-[2-(Dietilamino)etil]-5-[(5-fluoro-2-oxo-1,2-dihidro-3H-indol-3-iliden)metil]-2,4-dimetil-1H-pirrol-3-carboxamida (S)-2-hidroxisuccinato	Tratamiento de los tumores malignos del estroma gastrointestinal
Swedish	(Z)-N-[2-(Dietylamin)etyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-yliden)metyl]-2,4-dimetyl-1H-pyrrol-3-carboxamid (S)-2-hydroxysuccinat	Behandling av maligna gastrointestinala stromala tumörer
Norwegian	(Z)-N-[2-(Dietylamin)etyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-yliden)metyl]-2,4-dimetyl-1H-pyrrol-3-carboksamid (S)-2-hydroksysuksinat	Behandling av maligne gastrointestinale stromale tumorer
Icelandic	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1Hpyrrol-3-carboxamid (S)-2-hydroxysuccinat	Til meðferðar við grunnfrumuæxlum í meltingarfærum