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

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Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in July 2008 on request of the Sponsor.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-hydroxysyccinate for the treatment of renal cell carcinoma

On 10 March 2005, orphan designation (EU/3/05/268) 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-hydroxysyccinate for the treatment of renal cell carcinoma.

What is renal cell carcinoma?
Renal cell carcinoma (also called cancer of the kidney or renal adenocarcinoma) is a disease in which cancer (malignant) cells are found in certain tissues of the kidney. Inside each kidney are tiny tubules that filter and clean the blood, taking out waste products, and making urine. Renal cell carcinoma is a cancer of the lining of the tubules in the kidney. Renal cell carcinoma accounts for approximately 85% of all kidney cancers. Signs of cancer are difficult to detect in early stages of the disease, and about half of the patients are diagnosed when the disease has spread around the kidney or to distant parts of the body. Surgery is a common treatment of renal cell cancer, and allows taking out the cancer in an operation, although the cancer may appear again. Renal cell carcinoma is life-threatening.

What is the estimated number of patients affected by the condition?
At the time of designation, renal cell carcinoma affected approximately 3.5 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 161,000 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?
There are treatments for most patients with renal cell cancer. These may include surgery (taking out the cancer in an operation), chemotherapy (using drugs to kill cancer cells), radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells), hormone therapy (using hormones to stop cancer cells from growing), and biological therapy (using the body's immune system to fight cancer). The primary therapies for advanced renal cancer are biologic agents, such as interleukin-2 (IL-2) and interferon-α (IFN-α). Other anticancer agents had also been authorised in the Community for treatment of renal cell carcinoma at the time of submission of the application for orphan designation.

[*]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).

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Satisfactory argumentation has been submitted by the sponsor to justify the assumption that 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-hydroxysyccinate might be of potential significant benefit for the treatment of renal cell carcinoma mainly because it 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 orphan status.

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-hydroxysyccinate 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-hydroxysyccinate might, by inhibition of this enzyme activity, 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-hydroxysyccinate (Sutent) is authorised in the European Union as of 19 July 2006 for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.
Efficacy is based on objective response rates.
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	Autologous Tumor-Derived gp96 Heat Shock Protein-Peptide Complex	Treatment of renal cell carcinoma
Czech	Autologní, z tumoru derivovaný gp96 komplex peptidů a proteinů teplotního šoku	Léčba karcinomu ledvinných buněk
Danish	Autogent tumorafledt gp96 varmechok-protein-peptidkomplex	Behandling af renalcellekarcinom
Dutch	Autoloog tumoreus afgeleid gp96 hitteschok-protëine –peptidecomplex	Behandeling van niercelcarcinoom
Estonian	Autoloogiline kasvajast tuletatud gp96 kuumashoki valgu-peptiidi kompleks	Neeru vähi ravi
Finnish	Autologinen, kasvainperäinen, gp96-lämpösokkiproteiini-peptidi-kompleksi	Munuaiskarsinooman hoito
French	Complexe de protéine-peptide de choc thermique gp96, dérivé de cellules tumorales autologues	Traitement du carcinome rénal
German	Autologer, aus Tumorzellen gewonnener gp96 Hitzeschock-Protein-Peptidkomplex	Behandlung des Nierenzellkarzinoms
Greek	Αυτόλογο πρωτεϊνικό-πεπτιδικό σύμπλεγμα θερμικού πλήγματος gp96, προερχόμενο από νεόπλασμα	Θεραπεία του καρκινώματος νεφρών
Hungarian	Autológ tumor-eredetű gp96 hőshock fehérje-peptid komplex	Vesekarcinoma kezelése
Italian	Complesso proteina gp96-peptide da shock termico derivato da tumore autologo	Trattamento del carcinoma renale
Latvian	Autologs, no audzēja atvasināts gp96 karstumšoka olbaltumvielu-peptīdu komplekss	Nieru karcinomas ārstēšana
Lithuanian	Autologinis navikinės kilmės gp96 šiluminio streso baltymų ir peptidų kompleksas	Inkstų adenokarcinomos gydymas
Polish	Otrzymywany z tkanki nowotworowej autologiczny kompleks polipeptydów gp96 białek szoku cieplnego	Leczenie raka nerki
Portuguese	Complexo de proteínas/péptidos gp96 obtido por choque térmico, derivado de tumor autólogo	Tratamento do carcinoma das células renais
Slovak	Autologový, z tumoru získaný gp96 komplex peptidov a proteínov teplotného šoku	Liečba karcinómu obličky
Slovenian	Avtologni, iz tumorskih celic s toplotnim šokom pridobljen gp96 proteinsko-peptidni kompleks	zdravljenje raka ledvičnih celic
Spanish	Complejo péptido- proteína gp96 del shock térmico derivado de tumor autólogo	Tratamiento de carcinoma de células renales
Swedish	Autologt tumörderiverat gp96 värmechock protein-peptidkomplex	Behandling av njurcellscancer
Norwegian	Autologt tumor-derivert gp96-varmesjokkprotein-peptidkompleks	Behandling av nyrecellekarsinom
Icelandic	Samkynja gp96 hitalostmyndað prótínpeptíð samband úr æxli	Meðferð á nýrnafrumukrabbameini