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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate for the treatment of renal cell carcinoma

First publication	21 June 2010
Rev.1: transfer of sponsorship	16 March 2012
Rev.2: sponsor's change of address	12 June 2013
Rev.3: transfer of sponsorship	3 October 2014

Disclaimer

Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.

On 9 June 2010, orphan designation (EU/3/10/747) was granted by the European Commission to Aveo Pharma Ltd, United Kingdom, for N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate (also known as tivozanib) for the treatment of renal cell carcinoma.

The sponsorship was transferred to Astellas Pharma Europe B.V., The Netherlands, in March, 2012 and subsequently to AVEO Pharma Ltd, in September 2014.

What is renal cell carcinoma?

Renal cell carcinoma is a type of kidney cancer that originates in the cells lining the kidney tubules. These are small tubes that filter waste products out from the blood and make urine. Signs of renal cell carcinoma are difficult to detect in the early stages of the disease, and about half of the patients are diagnosed when the cancer has spread around the kidney or to other parts of the body.

Renal cell carcinoma is more common in men than in women. It is a life-threatening disease that is associated with poor long-term survival.

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

At the time of designation, renal cell carcinoma affected less than 4.2 in 10,000 people in the European Union (EU). This is equivalent to a total of fewer than 213,000 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 the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of designation, several medicines were authorised in the EU for the treatment of renal cell carcinoma. The main treatment was surgery, which was combined with radiotherapy (treatment with radiations) and chemotherapy (medicines to treat cancer) when the cancer had spread outside of the kidneys.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with renal cell carcinoma because it might improve the treatment of patients with this condition, and early studies in experimental models show that it might be more potent and more specific than existing treatments with similar mode of action. 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 some enzymes called 'tyrosine kinases' that are found in 'vascular endothelial growth factor' (VEGF) receptors. These receptors, which can be found on the surface of cancer cells, are involved in the development of new blood vessels that supply the tumours. By blocking VEGF receptors, this medicine is expected to slow down the growth of cancer cells by reducing their blood supply.

What is the stage of development of this medicine?

The effects of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate have been evaluated in experimental models.

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

At the time of submission, this medicine was not authorised anywhere in the EU for renal cell carcinoma 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 3 March 2010 recommending the granting of this 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 27), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 506,300,000 (Eurostat 2010).

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:

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www.aveooncology.com/contact-us

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[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate	Treatment of renal cell carcinoma
Bulgarian	N-{2-хлоро-4-[(6,7-диметокси-4-хинолил)окси]фенил}-N'-(5-метил-3-изоксазолил) урея хидрохлорид монохидрат	Лечение на бъбречно клетъчен карцином
Croatian	N-{2-kloro-4-[(6,7-dimetoksi-4-kinolil)oksi]fenil}-N´-(5-metil-3-izoksazolil)ureaklorid hidrat	Liječenje karcinoma bubrežnih stanica
Czech	N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]fenyl}-N'-(5-metyl-3-isoxazolyl) urea hydrochlorid monohydrát	Léčba karcinomu ledvin
Danish	N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]fenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochlorid monohydrate	Behandling af renalcellekarcinom
Dutch	N-{2-chloor-4-[(6,7-dimethoxy-4-quinolyl)oxy]fenyl}-N'-(5-methyl-3-isoxazolyl)ureumhydrochloride-monohydraat	Behandeling van niercelcarcinoom
Estonian	N-{2-kloro-4-[(6,7-dimetoksü-4-kinolüül)oksü]fenüül}-N'-(5-metüül-3-isoksasolüül) uurea vesinikkloriidmonohüdraat	Neeruvähi ravi
Finnish	N-{2-kloro-4-[(6,7-dimetoksi-4-kinolyyli)oksi]fenyyli}-N'-(5-metyyli-3-isoksatsolyyli) ureahydrokloridimonohydraatti	Munuaiskarsinooman hoito
French	Chlorhydrate de N-{2-chloro-4-[(6,7-diméthoxy-4-quinoléyl)oxy]phényl}-N'-(5-méthyl-3-isoxazolyl)urée monohydrate	Traitement du carcinome rénal
German	N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)-Harnstoff-Hydrochlorid-Monohydrat	Behandlung des Nierenzellkarzinoms
Greek	Μονοϋδρίτης της N-{2-χλωρο-4-[(6,7-διμεθοξυ-4-κινολυλ)οξυ]φαινυλ}-N'-(5-μεθυλ-3-ισοξαζολυλ) υδροχλωρικής ουρίας	Θεραπεία του νεφροκυτταρικού καρκινώματος
Hungarian	N-{2-kloro-4-[(6,7-dimetoxi-4-kinolil)oxi]fenil}-N'-(5-metil-3-izoxazolil) urea hidroklorid monohidrát	Vesekarcinoma kezelése
Italian	N-{2-cloro-4-[(6,7-dimetossi-4-chinolil)ossi]fenil}-N'-(5-metil-3-isossazolil) urea cloridrato monoidrato	Trattamento del carcinoma renale
Latvian	N-{2-hlor-4-[(6,7-dimetoksi-4-kvinolil)oksi]fenil}-N'-(5-metil-3-izoksazolil) karbamīda hidrohlorīda monohidrāts	Nieru karcinomas ārstēšana

[1] At the time of designation

Language	Active ingredient	Indication
Lithuanian	N-{2-chlor-4-[(6,7-dimetoksi-4-kvinolil)oksi]fenil}-N'-(5-metil-3-izoksazolil) karbamidhidrochlorido monohidratas	Inkstų adenokarcinomos gydymas
Maltese	N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate	Kura tal-karċinoma taċ-ċelluli renali
Polish	Chlorowodorek N-[2-chloro-4-(6,7-dimetoksy-4-chinoliloksy)fenylo]-N'-(5-metylo-3-izoksazolilo)mocznika jednowodny	Leczenie raka nerki
Portuguese	N-{2-cloro-4-[(6,7-dimetoxi-4-quinolil)oxi]fenil}-N'-(5-metil-3-isoxazolil) ureia cloridrato monohidrato	Tratamento de carcinoma das células renais
Romanian	N-{2-cloro-4-[(6,7-dimetoxi-4-chinolil)oxi]fenil}-N'-(5-metil-3-izoxazolil) uree clorhidrat monohidrat	Tratamentul carcinomului renal
Slovak	Monohydrát hydrochloridu N-{2-chlór-4-[(6,7-dimetoxy-4-chinolyl)oxy]fenyl}-N'-(5-metyl-3-izoxazolyl)-močoviny	Liečba karcinómu obličky
Slovenian	N-{2-kloro-4-[(6,7-dimetoksi-4-kinolil)oksi]fenil}-N'-(5-metil-3-izoksazolil) urea hidroklorid monohidrat	Zdravljenje raka ledvičnih celic
Spanish	N-{2-cloro-4-[(6,7-dimetoxi-4-quinolil)oxi]fenil}-N'-(5-metil-3-isoxazolil) urea hidrocloruro monohidrato	Tratamiento del carcinoma de células renales
Swedish	N-{2-klor-4-[(6,7-dimetoxi-4-kinolyl)oxi]fenyl}-N'-(5-metyl-3-isoxazolyl)ureahydrokloridmonohydrat	Behandling av njurcellscancer
Norwegian	N-{2-klor-4-[(6,7-dimetoksy-4-kinolyl)oksy]fenyl}-N'-(5-metyl-3-isoksazolyl) ureahydrokloridmonohydrat	Behandling av nyrecellekarsinom
Icelandic	N-{2-klóró-4-[(6,7-dímetoxý-4-kínólýl)oxý]fenýl}-N'-(5-metýl-3-ísoxasólýl) úrea hýdróklóríð einhýdrat	Meðferð á nýrnafrumukrabbameini