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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt for the treatment of medullary thyroid carcinoma

First publication	22 June 2009
Rev.1: transfer of sponsorship	19 September 2011
Rev.2: information about Marketing Authorisation	24 April 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 6 February 2009, orphan designation (EU/3/08/610) was granted by the European Commission to PPD Global Ltd, United Kingdom, for Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt for the treatment of medullary thyroid carcinoma.

The sponsorship was transferred to TMC Pharma Services Ltd, United Kingdom, in August 2011.

What is medullary thyroid carcinoma?

Thyroid carcinoma is a disease in which cancer (malignant) cells are found in certain tissues of the thyroid. The thyroid is a gland in the neck that is composed of mainly two different cell types: the follicular and parafollicular cells. The so-called follicular cells help to concentrate iodine and produce thyroid hormones. These hormones are important for the body's growth and metabolism. The parafollicular cells produce a hormone called calcitonin that reduces calcium level in the blood. Depending on the type of cell in which the cancer cells originate, different types of thyroid cancer exist.

Medullary thyroid carcinoma originates from the parafollicular cells (also called C cells), and represents only 5-9% of all thyroid cancers. Signs of cancer are difficult to detect in early stages of the disease and are often limited to a single local swelling of the thyroid gland which is not painful but can be felt by touching. Patients are frequently diagnosed when the disease has spread locally giving symptoms

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such as shortness of breath, difficulties in swallowing or changes in the voice. Some patients may have severe diarrhoea as a first sign of the disease.

Medullary thyroid carcinoma is a life-threatening disease.

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

At the time of designation, medullary thyroid carcinoma affected less than 0.7 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 35,000 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).

What treatments are available?

The treatment consists of a complete surgical removal of the thyroid. When patients can no longer be managed by surgery alone, various treatment approaches are tried. At the time of submission of the application for orphan drug designation, another medicine, doxorubicin, was authorised for the treatment of thyroid cancer in Sweden.

The sponsor has provided sufficient information to show that cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt might be of significant benefit for the patients because it might improve the long-term outcome of these patients. 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?

Enzymes are proteins produced by the human body that speed up the transformation of certain substances into other substances. Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate blocks (inhibits) a certain class of enzymes called tyrosine kinases. These enzymes play 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 cells. In medullary thyroid carcinoma, the function of some of these enzymes is disturbed causing uncontrolled growth and multiplication of the cancer cells. By inhibiting this enzyme activity, the product might help in slowing down or stopping the further growth of the cancer cells.

What is the stage of development of this medicine?

The effects of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt have been evaluated in experimental models.

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

At the time of submission, the medicinal product was not authorised anywhere in the world for medullary thyroid carcinoma or designated as 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 10 December 2008 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 504,800,000 (Eurostat 2009).

Update: Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt (Cometriq) has been authorised in the EU since 21 March 2014 for treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

More information on Cometriq can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

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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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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	Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt	Treatment of medullary thyroid carcinoma
Bulgarian	Циклопропан-1,1-дикарбоксилна киселина [4-(6,7-диметокси-квинолин-4-илокси)-фенил]-амид (4-флуоро-фенил)-амид, (L)-сол на ябълчената киселина	Лечение на медуларен карцином на щитовидната жлеза
Czech	[4-(6,7-dimetoxy-chinolin-4-yloxy)-fenyl]-amid (4-fluoro-fenyl)-amid, (L)-malátová sůl kyseliny cyklopropan-1,1-dikarboxylové	Léčba medulárního karcinomu štítné žlázy
Danish	Cyclopropan-1,1-dicarboxylsyre [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amid(4-fluor-phenyl)-amid, (L)-malatsalt	Behandling af medullært thyreoideakarcinom
Dutch	Cyclopropaan-1, 1-dicarbonzuur [4-(6,7-dimethoxy-chinolin-4-yloxy)-fenyl]-amide (4-fluoro-fenyl)-amide, (L)-malaat zout	Behandeling van medullair schildkliercarcinoom
Estonian	Tsüklopropaan-1,1-dikarboksüülhappe [4-(6,7-dimetoksükinoliin-4-üüloksü)fenüül]-amiid (4-fluorofenüül)-amiid, (L)-malaatsool	Medullaarse kilpnäärmevähi ravi
Finnish	Syklopropaani-1,1-dikarboksyylihappo [4-(6,7-dimetoksi-kinoliini-4-yloksi)fenyyli]-amidi (4-fluoro-fenyyli)-amidi, (L)-malaattisuola	Medullaarisen kilpirauhaskarsinooman hoito
French	(L)-Malate de l'acide cyclopropane-1,1-dicarboxylique [4-(6,7-diméthoxy-quinolin-4-yloxy)-phényl]-amide (4-fluoro-phényl)-amide	Traitement du cancer médullaire de la thyroïde
German	Cyclopropan-1,1-Dicarbonsäure [4-(6,7-Dimethoxy-quinolin-4-yloxy)-Phenyl]-amid (4-Fluorophenyl)-amid, (L)-Malat	Behandlung des medullären Schildrüsenkarzinoms
Greek	Κυκλοπροπάνιο-1,1-δικαρβοξυλικό οξύ [4-(6,7-διμεθοξυ-κινολινο-4-υλοξυ)-φαινυλο]-αμίδιο (4-φθοροφαινυλο)-αμίδιο, (L)-μηλικό άλας	Θεραπεία του μυελοειδούς καρκινώματος του θυρεοειδούς.
Hungarian	Ciklopropán-1,1-dikarbonsav [4-(6,7-dimetoxi-kinolin-4-iloxi)-fenil]amid (4-fluorfenil)amid, (L)-malát só	Medulláris thyroid carcinoma kezelése
Italian	Acido ciclopropan-1,1-dicarbossilico [4-(6,7-dimetossi-chinolin-4-ilossi)-fenil]-amide (4-fluoro-fenil)-amide, sale (L)-malato	Trattamento del carcinoma midollare della tiroide

[1] At the time of designation

Language	Active Ingredient	Indication
Latvian	Ciklopropāna-1,1-dikarboksilskābes [4-(6,7-dimetoksi-kvinolīn-4-iloksi)-fenil]-amīd (4-fluoro-fenil)-amīda, (L)-malāta sāls	Medulāras vairogdziedzera karcinomas ārstēšanai
Lithuanian	Ciklopropano-1,1-dikarboksilinė rūgštis [4-(6,7-dimetoksi-kvinolino-4-iloksi)-fenil]-amidas (4-fluorofenil)-amidas, (L)-malato druska	Medulinės skydliaukės karcinomos gydymas
Maltese	Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt	Kura tal-karċinoma tal-mudullun tat-tirojde
Polish	Cyklopropan-1,1-kwas dikarboksylowy [4-(6,7-dimetoksy-chinolino-4-yloksy)-fenyl]-amid (4-fluoro-fenyl)-amidu, (L)-sól kwasu maleinowego	Leczenie raka rdzeniastego tarczycy
Portuguese	Ácido ciclopropano-1,1-dicarboxílico [4-(6,7-dimetoxi-quinolina-4-iloxi)-fenil]-amida (4-fluoro-fenil)-amida, sal de (L)-malato	Tratamento do carcinoma medular da tiróide
Romanian	(L)-malat de ciclopropan-1,1-acid dicarboxilic [4-(6,7-dimetoxi-chinolin-4-iloxi)-fenil]-amidă (4-fluoro-fenil)-amidă	Tratamentul carcinomului medular tiroidian
Slovak	(L)-malát kyseliny cyklopropán-1,1-dikarboxylovej [4-(6,7-dimetoxychinolín-4-yloxy)-fenyl]-amid (4-fluórfenyl)-amid	Liečba medulárneho karcinómu štítnej žľazy
Slovenian	Ciklopropan-1,1-dikarboksilna kislina [4-(6,7-dimetoksi-kinolin-4-iloksi)-fenil]-amid (4-fluoro-fenil)-amid, (L)-malat	Zdravljenje medularnega karcinoma ščitnice
Spanish	Acido ciclopropano-1,1-dicarboxílico [4-(6,7-dimetoxi-quinolin-4-iloxi)-fenil]-amida (4-fluoro-fenil)-amida, sal del L-malato	Tratamiento del cáncer medular de tiroides
Swedish	Cyklopropan-1,1-dikarboxylsyra [4-(6,7-dimetoxikinolin-4-yloxi)-fenyl]-amid (4-fluorfenyl)-amid, (L)-malatsalt	Behandling av medullär thyreoideacancer
Norwegian	Syklopropan-1,1-dikarboksylsyre [4-(6,7-dimetoksy-kinolin-4-yloksy)-fenyl]-amid (4-fluorofenyl)-amid, (L)-malatsalt	Behandling av medullært thyreoideacarcinom
Icelandic	Cýklóprópan-1,1-díkarboxýlsýru [4-(6,7-dímetoxý-kínólín-4-ýloxý)-fenýl]-amíð (4-flúoró-fenýl)-amíð, (L)-malatsalt	Meðferð á merggerðarkrabbameini í skjaldkirtli