16 September 2019
EMADOC-628903358-1034

Public summary of opinion on orphan designation

(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride for the treatment of maternally inherited diabetes and deafness

On 28 June 2019, orphan designation EU/3/19/2168 was granted by the European Commission to Khondrion B.V., the Netherlands, for (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride (also known as KH176) for the treatment of maternally inherited diabetes and deafness.

What is maternally inherited diabetes and deafness?

Maternally inherited diabetes and deafness is a type of diabetes inherited from the mother, often accompanied by hearing loss. Other symptoms include macular retinal dystrophy (an eye disorder that causes vision loss), muscle weakness, heart and kidney problems and constipation.

In most cases, the disease develops in early adulthood and is caused by mutations (changes) in the DNA (genetic material) of mitochondria (energy-producing components of cells). As a result, mitochondria do not function well and cells cannot perform their functions correctly. The disease affects the organs where cells are most active such as the pancreas, causing problems with the release of insulin into the blood and leading to diabetes. As mitochondria are also very active in the cochlea (part of the inner ear) it also affects hearing.

Maternally inherited diabetes and deafness is a long-term debilitating disease due to deafness and difficult to treat diabetes.

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

At the time of designation, maternally inherited diabetes and deafness affected less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 52,000 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 518,400,000 (Eurostat 2019).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for the treatment of maternally inherited diabetes and deafness. Patients were given medicines for diabetes and hearing aids.

How is this medicine expected to work?

The defects in mitochondria that occur in maternally inherited diabetes and deafness are known to result in the production of toxic molecules containing oxygen that cause damage to cells (known as 'oxidative stress'). The medicine is a small molecule capable of entering the cell where it acts as an antioxidant, reducing oxidative stress. This antioxidant activity is expected to reduce the symptoms of the disease.

What is the stage of development of this medicine?

The effects of (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with maternally inherited diabetes and deafness were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of maternally inherited diabetes and deafness. Orphan designation of the medicine had been granted in the United States for the treatment of inherited mitochondrial respiratory chain diseases.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 23 May 2019, 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.

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	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride	Treatment of maternally-inherited diabetes and deafness
Bulgarian	(S)-6-хидрокси-2,5,7,8-тетраметил-N-((R)-пиперидин-3-ил)хроман-2-карбоксамид хидрохлорид	Лечение на наследени по майчина линия диабет и глухота
Croatian	(S)-6-hidroksi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)kroman-2-karboksamid hidroklorid	Liječenje maternalno naslijeđenog dijabetesa i gluhoće
Czech	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-karboxamid hydrochlorid	Léčba maternálně dědičného diabetu a hluchoty
Danish	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamidhydrochlorid	Behandling af maternelt nedarvet diabetes og døvhed
Dutch	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chromaan-2-carboxamidehydrochloride	Behandeling van maternaal overerfbare diabetes en doofheid
Estonian	(S)-6-hüdroksü-2,5,7,8-tetrametüül-N-((R)-piperidiin-3-üül)kromaan-2-karboksamiid vesinikkloriid	Emalt päritud suhkurtõve ja kurtuse ravi
Finnish	(S)-6-hydroksi-2,5,7,8-tetrametyyli-N-((R)-piperidin-3-yyli)kromaani-2-karboksiamidihydrokloridi	Äidiltä periytyvän diabeteksen ja kuurouden hoito
French	Chlorhydrate de (S)-6-hydroxy-2,5,7,8-tétraméthyl-N-((R)-pipéridine-3-yl)chroman-2-carboxamide	Traitement du diabète-surdité de transmission maternelle
German	(S)-6-Hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamidhydrochlorid	Behandlung von durch die Mutter vererbtem Diabetes und Taubheit
Greek	υδροχλωρικό (S)-6-υδροξυ-2,5,7,8-τετραμεθυλ-N-((R)-πιπεριδιν-3-υλ)χρωμαν-2-καρβοξαμίδιο	Θεραπεία μητρικά κληρονομούμενου διαβήτη και κώφωσης
Hungarian	(S)-6-hidroxi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)króman-2-karboxamid-hidroklorid	Anyai ágon öröklődő diabetes és süketség kezelése
Italian	(S)-6-idrossi-2,5,7,8-tetrametil-N-((R)-piperidina-3-il)croman-2-carbossamide cloridrato	Trattamento del diabete e della sordità ereditati per via materna
Latvian	(S)-6-hidroksi-2,5,7,8-tetrametil-N-((R)-piperidīn-3-il)hromān-2-karboksamīda hidrohlorīds	Maternāli pārmantota diabēta un kurluma ārstēšana

[1] At the time of designation

Language	Active ingredient	Indication
Lithuanian	(S)-6-hidroksi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)chroman-2-karboksamido hidrochloridas	Iš motinos paveldėto diabeto ir kurtumo gydymas
Maltese	(S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride	Kura ta' dijabete u truxija li jintirtu maternalment
Polish	Chlorowodorek (S)-6-hydroksy-2,5,7,8-tetrametylo-N-((R)-piperydyno-3-ylo)chromano-2-karboksyamidu	Leczenie dziedziczonej po matce cukrzycy z głuchotą
Portuguese	Cloridrato de (S)-6-hidroxi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)croman-2-carboxamida	Tratamento de diabetes e surdez com hereditariedade materna
Romanian	Clorhidrat de (S)-6-hidroxi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)croman-2-carboxamidă	Tratamentul diabetului zaharat și surdităţii moștenite de la mamă (diabet MIDD)
Slovak	(S)-6-hydroxy-2,5,7,8-tetrametyl-N-((R)-piperidín-3-yl)chróman-2-karboxamid hydrochlorid	Liečba matrilineárne zdedeného diabetes mellitus a hluchoty
Slovenian	(S)-6-hidroksi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)kroman-2-karboksamid hidroklorid	Zdravljenje po materi podedovane sladkorne bolezni in gluhote
Spanish	(S)-6-hidroxi-2,5,7,8-tetrametil-N-((R)-piperidin-3-il)croman-2-carboxamida hidrocloruro	Tratamiento de la diabetes y sordera heredadas por vía materna
Swedish	(S)-6-hydroxi-2,5,7,8-tetrametyl-N-((R)-piperidin-3-yl)kroman-2-karboxamidhydroklorid	Behandling av maternellt ärvd diabetes och dövhet
Norwegian	(S)-6-hydroksy-2,5,7,8-tetrametyl-N-((R)-piperidin-3-yl)-kroman-2-karboksamidhydroklorid	Behandling for diabetes og hørselstap nedarvet fra moren
Icelandic	(S)-6-hýdroxý-2,5,7,8-tetrametýl-N-((R)-píperidín-3-ýl)króman-2-karboxamíð hýdróklóríð	Meðferð við sykursýki ásamt heyrnarleysi sem erfist frá móður