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Public summary of opinion on orphan designation

2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione for the treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

On 12 December 2017, orphan designation (EU/3/17/1947) was granted by the European Commission to NeuroVive Pharmaceutical AB, Sweden, for 2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione (also known as KL1333) for the treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.

What is mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)?

MELAS is an inherited disease caused by genetic abnormalities in the mitochondria, the energy-producing components within cells. Symptoms of the condition usually appear in childhood and include muscle weakness and pain, headaches, loss of appetite, vomiting and seizures (fits). By the age of 40, most patients experience stroke-like episodes that can lead to vision loss, problems with movement and loss of intellectual function.

The condition is life threatening and debilitating in the long term due to symptoms such as seizures, stroke-like episodes, and the recurring headaches, vomiting and weakness.

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

At the time of designation, MELAS affected approximately 0.06 in 10,000 people in the European Union (EU). This was equivalent to a total of around 3,000 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?

No satisfactory methods of treatment were authorised in the EU at the time of orphan designation. Patients received supportive therapy to deal with the symptoms.

[*]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 515,700,000 (Eurostat 2017).

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How is this medicine expected to work?

The medicine works by combining with an enzyme widely present in body cells and triggering the production of NAD^+ inside the cell. The increase in NAD^+ triggers the activation of several proteins and cell processes which are expected to improve the function of mitochondria. Because MELAS is linked to abnormalities in the mitochondria, improvements in mitochondrial function are expected to help reduce symptoms of the condition.

What is the stage of development of this medicine?

The effects of the medicine 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 MELAS had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for MELAS 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 31 October 2017 recommending the granting of this designation.

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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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's rare disease designations page.

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	2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione	Treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
Bulgarian	2-изопропил-3H-нафто[1,2-d]имидазол-4,5-дион	Лечение на митохондриална енцефаломиопатия, лактатна ацидоза и инсулт подобни епизоди
Croatian	2-isopropil-3H-nafto[1,2-d]imidazol-4,5-dion	Liječenje mitohondijske encefalomiopatije, laktične acidoze i epizoda nalik na moždani udar
Czech	2-isopropyl-3H-naftol/1,2-D/imidazol-4,5-dion	Léčba mitochodnriální encefalomyopatie, laktátové acidózy a iktoidní episody
Danish	2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione	Behandling af MELAS syndrom (mitokondriel myopati, encephalopati, mælkesyreose og slagtilfælde)
Dutch	2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione	Behandeling van mitochondriale encephalomyopathy, lactaatacidosis en neurologische beroerte-achtige episodes
Estonian	2-isopropüül-3H-nafto[1,2-d]imidazool-4,5-dioon	Mitokondriaalse entsefalomüopaatia, laktaatatsidoosi ja insuldisarnaste episoodide ravi
Finnish	2-isopropyyli-3H-nafto[1,2-d]imidatsoli-4,5-dioni	Mitokondriaalisen enkefalomyopatian, maitohappoasidoosin ja kohtauksellisten aivoverenkiertohäiriöitä muistuttaven aivotoiminnan häiriöiden hoito
French	2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione	traitement de l'encéphalomyopathie mitochondriale, l'acidose lactique et des épisodes stroke-like
German	2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dion	Behandlung von mitochondriale Enzephalopathie, Laktatazidose und Schlaganfall-ähnliche Episoden
Greek	2-ισοπροπυλο-3H-ναφθο[1,2-d]ιμιδαζολο-4,5-διόνη	Θεραπεία της μιτοχοχονδριακής εγκεφαλομυοπάθειας, γαλακτικής οξέωσης και επεισοδείων που ομοιάζουν εγκεφαλικών (σύνδρομο MELAS)
Hungarian	2-isopropyl-3H-naphtho[1,2-d]imidazol-4,5-dion	Mitokondriális enkefalomiopátia, laktátacidózis és stroke-szerű epizódok kezelése
Italian	2-isopropil-3H-naftol[1,2-d]imidazol-4,5-dione	Trattamento dell'encefalomiopatia mitocondriale con acidosi lattica ed episodi tipo ictus
Latvian	2-izopropil-3H-nafto[1,2-d]imidazol-4,5-dions	Mitohondriālās encefalomiopātijas, pienskābās acidozes un insultam līdzīgo epizožu ārstēšana
Lithuanian	2-izopropil-3H-nafto[1,2-d]imidazolo-4,5-dionas	Mitochondrinės encefalomiopatijos, laktatacidozės ir į insultą panašių priepuolių epizodų gydymas
Maltese	2-isopropil-3H-nafto[1,2-d]imidażol-4,5-dion	Kura ta' enċefalomijopatija mitokondrijali, aċidoż i lattika u episodji li jixbhu lill-attakki ta' puplesija
Polish	2-izopropylo-3H-nafto[1,2-d]imidazolo-4,5-dion	Leczenie zespołu miopatii mitochondrialnej, encefalopatii, kwasicy mleczanowej oraz występowania incydentów podobnych do udarów
Portuguese	2-isopropil-3*H*-nafto[1,2-*d*]imidazol-4,5-diona	Tratamento da encefalomiopatia mitocondrial, acidose lática e episódios do tipo acidente vascular cerebral

[1] At the time of designation

Language	Active ingredient	Indication
Romanian	2-izopropil-3H-nafto[1,2-d]imidazole-4,5-dionă	Tratamentul encefalomiopatiei mitocondriale, acidozei lactice şi al episoadelor de tip accident vascular cerebral
Slovak	2-izopropyl-3H-nafto[1,2-d]imidazol-4,5-dión	Liečba mitochondriálnej encefalomyopatie, laktátovej acidózy a infarktu podobných epizód
Slovenian	2-izopropil-3H-nafto[1,2-d]imidazol-4,5-dione	Zdravljenje mitohondijske encefalomiopatije, laktacidoze in kapi podobnih epizod
Spanish	2-isopropil-3H-nafto[1,2-d]imidazole-4,5-dione	Tratamiento de la encefalomiopatía mitocondrial, acidosis láctica y episodios tipo ictus
Swedish	2-isopropyl-3H-naftho[1,2-d]imidazol-4,5-dion	Behandling av mitokondriell hjärn- och muskelsjukdom med stegrad mjölksyrahalt i blodet och strokeliknande attacker
Norwegian	2-isopropyl-3H-nafto[1,2-d]imidazol-4,5-dion	Behandling av mitokondrie encefalomyopati, laktacidose og slagliknende episoder
Icelandic	‘Isóprópýl-3H naphtó[1,2-d] ímídazól-4,5-díón	Meðferð hvatbera heilavöðvakvilla, mjólkursýringu og heilaáfalls- líkum köstum