



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

9 January 2020  
EMADOC-628903358-1521

## Public summary of opinion on orphan designation

(S)-2-Isobutyrylamino-pentanedioic acid 5-amide 1-  
{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide} for the treatment of Netherton syndrome

On 17 October 2019, orphan designation EU/3/19/2203 was granted by the European Commission to MDC RegAffairs GmbH, Germany, for (S)-2-isobutyrylamino-pentanedioic acid 5-amide 1-  
{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide} (also known as LM-030) for the treatment of Netherton syndrome.

### What is Netherton syndrome?

Netherton syndrome is an inherited skin condition in which the patient, usually a newborn baby, has red, scaly skin, which cannot properly protect against infection or retain heat, water and proteins. Many babies also have a 'bamboo-type' hair structure, with strands of varying diameter. Babies born with the syndrome may fail to thrive in their first years of life and die due to infections.

Netherton syndrome is caused by a change in the gene responsible for producing a protein called LEKT1, which regulates the action of enzymes called kallikreins. Kallikreins are involved in the shedding of the skin. As a result of the change in the LEKT1 gene, kallikreins become overactive, causing excessive shedding and damage to the skin.

Netherton syndrome is a long-term debilitating and life-threatening condition because of the skin damage and associated infections, and failure to thrive.

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

At the time of designation, Netherton syndrome affected approximately 0.04 in 10,000 people in the European Union (EU). This was equivalent to a total of around 2,000 people\*, and is below the ceiling

---

\*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](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European Union



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 submission for orphan designation, no satisfactory methods were authorised in the EU for the treatment of Netherton syndrome. To reduce the inflammation of the skin in patients with Netherton syndrome, creams containing medicines such as steroids and calcineurin inhibitors were used in addition to general moisturisers and emollients (substances that soften or smooth the skin). For severe forms of the disease, medicines injected in a vein to reduce inflammation were also used.

### **How is this medicine expected to work?**

The medicine blocks the action of a group of enzymes called serine proteases, which include kallikreins. By blocking kallikerins, the medicine, which is expected to be applied on the skin, is thought to reduce excessive shedding and damage to the skin.

### **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, clinical trials with the medicine in patients with Netherton syndrome were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of Netherton syndrome or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 12 September 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<sup>1</sup>, Norwegian and Icelandic

Language	Active ingredient	Indication
English	(S)-2-isobutyrylamino-pentanedioic acid 5-amide 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide}}	Treatment of Netherton syndrome
Bulgarian	(S)-2-изобутириламино-пентандионова киселина 5-амид 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-дву-((S)-вторичен-бутил)-21-хидрокси-5-(4-хидрокси-бензил)-15-изобутил-4,11-диметил-3,6,9,13,16,22-хексаоксо-10-окса-1,4,7,14,17-пентааза-двущикличен[16.3.1]докос-12-ил]-амид}	Лечение на синдрома на Netherton
Croatian	(S)-2-izobutirilamino-pentanska dikiselina 5-amid 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butyl)-21-hidroksi-5-(4-hidroksi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaaza-biciklo[16.3.1]dokos-12-il]} -amid}	Liječenje Nethertonovog sindroma
Czech	5-amid kyseliny (S)-2-isobutyrylamino-pentandiové 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxybenzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyklo[16.3.1]dokos-12-yl]-amid}	Léčba Nethertonova syndromu
Danish	(S)-2-Isobutyrylamin-pentadisyre 5-amid 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amid}	Behandling af Nethertons syndrom
Dutch	(S)-2-Isobutyrylamino-pentanedioic zuur5-amide 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide}}	Behandeling van het syndroom van Netherton

<sup>1</sup> At the time of designation

Language	Active ingredient	Indication
Estonian	(S)-2-isobutürüülamino-pentaandihappe 5-amiid-1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butüül)-21-hüdrosü-5-(4-hüdrosü-bensüül)-15-isobutüül-4,11-dimetüül-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaasa-bitsüklo[16.3.1]dokos-12-üül]-amiid}}	Nehtertoni sündroomi ravi
Finnish	(S)-2-isobutyryyliaminopentaanihapon 5-amidi 1 -{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyylä)-21-hydroksi-5-(4-hydroksibentsyyli)-15-isobutyylä-4,11-dimetyyli-3,6,9,13,16,22-hexaokso-10-oksa-1,4,7,14,17-penta-atsa-bisyklo[16.3.1]dokos-12-yyli]amidi}}	Nethertonin oireyhtymän hoito
French	(S)-acide 2-Isobutyrylamino-pentane dioïque 5-amide 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxybenzyl)-15-isobutyl-4,11-diméthyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide}}	Traitement du syndrome de Netherton
German	(S)-2-isobutyrylaminopentandisäure-5-amid-1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxybenzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amid}}	Behandlung des Netherton Syndroms
Greek	(S)-2-ισοβουτυρυλαμινό-πεντανοδιοϊκό οξύ 5-αμίδιο 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-δισ-((S)-δευτεροταγές-βουτύλιο)-21-υδροξυ-5-(4-υδροξυ-βενζυλο)-15-ισοβουτύλιο-4,11-διμεθυλ-3,6,9,13,16,22-εξαοξο-10-όξα-1,4,7,14,17-πεντααζα-δικυκλο[16.3.1]δοκο-12-ακυλ]-αμίδιο}}	Θεραπεία του συνδρόμου Netherton
Hungarian	(S)-2-izobutiril-amino-pentándisav-5-amid-1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bisz-((S)-szek-butil)-21-hidroxi-5-(4-hidroxi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-biciklo[16.3.1]dokoz-12-il]-amid}}	Netherton szindróma kezelése

Language	Active ingredient	Indication
Italian	(S)-acido 2-isobutirilamino-pentanedioico 5-ammide 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butile)-21-idrossi-5-(4-benzil-idrossi)-15-isobutil-4,11-dimetil-3,6,9,13,16,22-hexaoxa-10-ossa-1,4,7,14,17-pentaaza-biciclo[16.3.1]docos-12-yl]-ammide}	Trattamento della sindrome di Netherton
Latvian	(S)-2-izobutirilamīna-pentāndiskābes 5-amīdu 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butil)-21-hidroksi-5-(4-hidroksi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-heksokso-10-oksa-1,4,7,14,17-pentaaza-biciklo[16.3.1]dokos-12-īl]-amīds}	Netertona sindroma ārstēšana
Lithuanian	(S)-2-izobutirilamino-pentanedioik rūgštis 5-amidas 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butil)-21-hidroksi-5-(4-hidroksi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaza-biciklo[16.3.1]dokos-12-il]-amidas}	Nethertono sindromo gydymas
Maltese	(S)-2-isobutirilammino-aċidu pentanediojku 5-ammid 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butil)-21-idrossi-5-(4-idrossi-benzil)-15-isobutil-4,11-dimetil-3,6,9,13,16,22-hexaoosso-10-ossa-1,4,7,14,17-pentaaza-biciklo[16.3.1]dokos-12-il]-ammid}	Kura tas-sindrome ta' Netherton
Polish	5-amid 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butyl)-21-hydroksy-5-(4-hydroksy-benzyl)-15-izobutyl-4,11-dimetylo-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaaza-bicyklo[16.3.1]dokozylo]-amid} kwasu (S)-2-izobutyryloamino-pentanodionowego	Leczenie zespołu Nethertona
Portuguese	Ácido (S)-2-isobutirilamino-pentanodióico 5-amida 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hidroxi-5-(4-hidroxi-benzil)-15-isobutil-4,11-dimetil-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-biciclo[16.3.1]docos-12-il]-amida}	Tratamento da síndrome de Netherton
Romanian	(S)-2-acid izobutirilamino-pentandioic 5-amido 1- {[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hidroxi-5-(4-hidroxi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-biciclo[16.3.1]docos-12-il]-amidă}	Tratamentul sindromului Netherton

Language	Active ingredient	Indication
Slovak	(S)-2-izobutyrylamino-pentándiová kyselina 5-amid 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sek-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-izobutyl-4,11-dimetyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyklo[16.3.1]dokos-12-yl]-amid}}	Liečba Nethertonovho syndrómu
Slovenian	(S)-2-izobutirilamino-pentandiojska kislina 5-amid 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis--((S)-sec-butyl)-21-hidroksi-5-(4-hidroksi-benzil)-15-izobutil-4,11-dimetil-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaaza-biciklo[16.3.1]dokos-12-il]-amid}}	Zdravljenje Nethertonovega sindroma
Spanish	(S)-2-Isobutirilamino- ácido pentanodioico 5-amida 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butilo)-21-hidroxi-5-(4-hidroxi-bencil)-15-isobutil-4,11-dimetil-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-biciclo[16.3.1]docos-12-il]-amida}}	Tratamiento del síndrome de Netherton
Swedish	(S)-2-isobutyrylamino-pentandisyra 5-amid 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxi-5-(4-hydroxi-bensyl)-15-isobutyl-4,11-dimetyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyklo[16.3.1]docos-12-yl]-amid}}	Behandling av Nethertons syndrom
Norwegian	(S)-2-isobutyrylamino-pentandisyre 5-amid 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis -((S)-sekbutyl)-21-hydroksy-5-(4-hydroksy-benzyl)-15-isobutyl-4,11-dimetyl-3,6,9,13,16,22-heksaokso-10-oksa-1,4,7,14,17-pentaaza-bisyklo[16.3.1]dokos-12-yl]-amid}}	Behandling av Nethertons syndrom
Icelandic	(S)-2-ísóbútýrýlamíno-glútarsýra 5-amíð 1-{{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-bútan-2-ýl)-21-hýdroxý-5-(4-hýdroxý-benzýl)-15-ísóbútýl-4,11-dímetýl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bísýkló[16.3.1]dókos-12-ýl]-amíð}}	Meðhöndlun á Netherton heilkenni