



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2020
EMADOC-628903358-1674

Public summary of opinion on orphan designation

Adeno-associated virus vector encoding human phenylalanine hydroxylase for the treatment of phenylalanine hydroxylase deficiency

On 16 December 2019, orphan designation EU/3/19/2229 was granted by the European Commission to BioMarin International Limited, Ireland, for adeno-associated virus vector encoding human phenylalanine hydroxylase (also known as BMN 307) for the treatment of phenylalanine hydroxylase deficiency.

What is phenylalanine hydroxylase deficiency?

Phenylalanine hydroxylase deficiency is a condition in which the body cannot process phenylalanine, an amino acid found in dietary proteins, because an enzyme called phenylalanine hydroxylase is lacking. This causes phenylalanine to build up in the blood to harmful levels and can lead to brain damage and impair normal development.

Phenylalanine hydroxylase deficiency is debilitating in the long-term because of its effects on the brain in patients who are not treated.

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

At the time of designation, phenylalanine hydroxylase deficiency affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 104,000 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?

At the time designation, Kuvan (sapropterin) and Palynziq (pegvaliase) were authorised in the EU to treat high blood levels of phenylalanine. In addition, because phenylalanine can only come from the diet, avoiding foods containing phenylalanine has been an important part of treatment.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with phenylalanine hydroxylase deficiency. This is because laboratory studies

*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).



showed that a single dose of the medicine is able to lower levels of phenylalanine in the blood and keep levels low for a long time, meaning that patients would not need regular treatment. 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?

Patients with phenylalanine hydroxylase deficiency cannot process phenylalanine in the usual way because of mutations (changes) in the gene for the enzyme phenylalanine hydroxylase. This medicine is made of a virus that contains normal copies of the gene for phenylalanine hydroxylase. When given to the patient, it is expected that the virus will be carried into the patient's cells enabling them to start producing the enzyme. This is expected to reduce levels of the amino acid in the blood, improving the symptoms of the disease.

The type of virus used in this medicine ('adeno-associated virus') does not cause disease in humans.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of the medicine in experimental models was ongoing.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with phenylalanine hydroxylase deficiency had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of phenylalanine hydroxylase deficiency 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 15 November 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

Language	Active ingredient	Indication
English	Adeno-associated virus vector encoding human phenylalanine hydroxylase	Treatment of phenylalanine hydroxylase deficiency
Bulgarian	Адено-асоцииран вирусен вектор, кодиращ човешка фенилаланин хидроксилаза	Лечение на фенилаланин хидроксилазна недостатъчност
Croatian	Adeno-vezani virusni vektor koji kodira ljudsku fenilalanin hidrosilazu	Liječenje nedostatka fenilalanin hidrosilaze
Czech	Adeno-asociovaný virový vektor kódující lidskou fenylalaninhydroxylázu	Léčba fenylalanin hydroxylázového deficit
Danish	Adenoassocieret virusvektor, der koder for human phenylalaninhydroxylase	Behandling af phenylalanin hydroxylase mangel
Dutch	Adeno-geassocieerde virale vector die humaan fenylalaninehydroxylase codeert	Behandeling van phenylalanine hydroxylase deficiëntie
Estonian	Inimese fenüülalaniini hüdroksülaasi kodeeriv adeno-assotsieerunud viirusvektor	Fenüülalaniini hüdroksülaasi puudulikkuse ravi
Finnish	Adenoassosioitu virusvektori, joka koodaa ihmisen fenyyilalaniinihydroksylaasia	Fenyyilalaniinihydroksylaasin puutteen hoito
French	Vecteur viral adéno-associé codant la phénylalanine hydroxylase humaine	Traitement de la déficience en phénylalanine hydroxylase
German	Adeno-assoziiertes Virusvektor, der für humane Phenylalaninhydroxylase kodiert	Behandlung der Phenylalanine Hydroxylase Defizienz
Greek	Φορέας αδενοσχετιζόμενου ιού που κωδικοποιεί την ανθρώπινη υδροξυλάση της φαινυλαλανίνης	Θεραπεία της ανεπάρκεια της υδροξυλάσης της φαινυλαλανίνης
Hungarian	Humán fenilalanin-hidroxiláz kódoló adeno-asszociált vírus vektor	Fenilalanin-hidroxiláz elégtelenség kezelése
Italian	Vettore virale adeno-associato codificante la fenilalanina idrossilasi umana	Trattamento del deficit di fenilalaninidrossilasi
Latvian	Adeno saistītā vīrusa vektors, kas kodē cilvēka fenilalanīna hidroksilāzi	Fenilalanīna hidroksilāzes nepietiekamības ārstēšana
Lithuanian	Adeno asocijuoto viruso vektorius, koduojantis žmogaus fenilalanino hidroksilazę	Fenilalanino hidroksilazės stokos gydymas
Maltese	Vettur tal-virus assoċjat ma' adeno li jikkodifika l-fenilalanina idrossilażi umana	Kura ta' defiċjenza ta' fenilalanina idrossilażi
Polish	Związany z adenowirusami wektor wirusowy kodujący ludzką hydroksylazę fenyloalaninową	Leczenie niedoboru hydroksylazy fenyloalaninowej

Language	Active ingredient	Indication
Portuguese	Vetor viral adeno-associado que codifica a fenilalanina hidroxilase humana	Tratamento da deficiência de fenilalanina hidroxilase
Romanian	Vector viral adeno-asociat care codifică fenilalaninhidroxilaza umană	Tratamentul deficitului de fenilalaninhidroxilază
Slovak	Adeno-asociovaný vírusový vektor kódujúci ľudskú fenylalanínhydroxylázu	Liečba deficiencie fenylalanín hydroxylázy
Slovenian	Adenovirusom pridruženi vektor, ki kodira človeško fenilalanin hidroksilazo	Zdravljenje pomanjkanja hidroksilaze fenilalanina
Spanish	Vector de virus adenoasociado codificador de fenilalanina hidroxilasa humana	Tratamiento de la deficiencia de fenilalanina hidroxilase
Swedish	Adenoassocierad virusvektor som kodar humant fenylalaninhidroxilas	Behandling av fenylalanin-hydroxylasebrist
Norwegian	Adenoassosiert virusvektor som koder for human fenylalaninhidroksylase	Behandling av fenylalanin hydroksylase mangel
Icelandic	Adenótengd veirugenaferja sem kóðar fyrir fenýlalanínhýdroxýlasa úr mönnum	Meðferð við fenýlalanín hýdroxýlasaskorti