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Public summary of opinion on orphan designation

Adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase for the treatment of phenylalanine hydroxylase deficiency

On 14 December 2018, orphan designation (EU/3/18/2109) was granted by the European Commission to Yes Pharmaceutical Development Services GmbH, Germany, for adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase (also known as HMI-102) 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 fewer than 103,000 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) was authorised in the EU to treat high blood levels of phenylalanine. In addition, because phenylalanine can only come from the diet, dietary restriction 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. Early laboratory studies have shown

*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 517,400,000 (Eurostat 2018).

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that a single injection could normalise phenylalanine levels in the blood and reduce the need to use the currently authorised 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 usually because of mutations (changes) in the gene for 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 and thereby reduce levels of the amino acid in the blood.

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?

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 phenylalanine hydroxylase deficiency had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for phenylalanine hydroxylase deficiency. Orphan designation of the medicine had been granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 November 2018 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 the 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	Adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase	Treatment of phenylalanine hydroxylase deficiency
Bulgarian	Адено-асоцииран вирус, серотип HSC15, експресиращ човешка фенилаланин хидроксилаза	Лечение на фенилаланин хидроксилазна недостатъчност
Croatian	Adeno-povezani virus serotipa HSC15 koji eksprimira humanu fenilalanin hidroksilazu	Liječenje nedostatka fenilalanin hidroksilaze
Czech	Adeno- asociovaný virus serotypu HSC15 exprimující humánní fenylalalnin hydroxylásu	Léčba fenylalanin hydroxylázového deficitu
Danish	Adeno-associeret virus serotype HSC15, der udtrykker human phenylalaninhydroxylase	Behandling af phenylanalin hydroxylase mangel
Dutch	Adeno-geassociëerd virus serotype HSC15 welke humaan phenylalanine hydroxylase uitdrukt	Behandeling van phenylalanine hydroxylase deficiëntie
Estonian	Inimese fenüülalaniini hüdroksülaasi ekspresseeriv adeno-assotsieerunud viirusvektori serotüüp HSC15	Fenüülalaniini hüdroksülaasi puudulikkuse ravi
Finnish	Adenoassosioitu serotyypin HSC15 virus, joka ilmentää ihmisen fenyylialaniinihydroksylaasia	Fenyylialaniinihydroksylaasin puutteen hoito
French	Virus adéno-associé de sérotype HSC15 exprimant la phénylalanine hydroxylase humaine	Traitement de la déficience en phénylalanine hydroxylase
German	Adeno-assoziierter Virus vom Serotyp HSC15 der humane Phenylalanine Hydroxylase expremiert	Behandlung der Phenylalanine Hydroxylase Defizienz
Greek	Αδενο-σχετιζόμενος ιός οροτύπου HSC15 που εκφράζει την ανθρώπινη υδροξυλάση της φαινυλαλανίνης	Θεραπεία της ανεπάρκεια της υδροξυλάσης της φαινυλαλανίνης
Hungarian	Humán fenilalanin-hidroxilázt expresszáló HSC15 fenotípusú adeno-asszociált virus vektor	Fenilalanin-hidroxiláz elégtelenség kezelése
Italian	Virus adeno-associato di serotipo HSC15 che esprime lafenilalaninidrossilasi umana	Trattamento del deficit di fenilalaninidrossilasi
Latvian	Adeno-asociētā vīrusa serotips HSC15, kas ekspresē cilvēka fenilalanīna hidroksilāzi	Fenilalanīna hidroksilāzes nepietiekamības ārstēšana
Lithuanian	Adeno asocijuoto viruso serotipas HSC15, ekspresuojantis žmogaus fenilalanino inhidroksilazę	Fenilalanino hidroksilazės stokos gydymas
Maltese	Serotip HSC15 tal-virus assoċjat ma' adeno li jesprimi fenilalanina idrossilaži umana	Kura ta' defiċjenza ta' fenilalanina idrossilaži
Polish	Wirus związany z adonowirusami serotypu HSC15 eksprymujący ludzką hydroksylazę fenyloalaninową	Leczenie niedoboru hydroksylazy fenyloalaninowej
Portuguese	Vírus adeno-associado de serotipo HSC15 expressando a fenilalanina hidroxilase humana	Tratamento da deficiência de fenilalanina hidroxilase

[1] At the time of designation

Language	Active ingredient	Indication
Romanian	Virus adeno-ascoiat de serotip HSC15 ce exprimă fenilalaninhidroxilaza umană	Tratamentul deficitului de fenilalaninhiroxilază
Slovak	Adeno-asociovaný vírus sérotypu HSC15 exprimujúci ľudskú fenylalanín hydroxylázu	Liečba deficiencie fenylalanín hydroxylázy
Slovenian	Adeno-pridruženi virusni vektor serotipa HSC15, ki eksprimira človeško hidroksilazo fenilalanina	Zdravljenje pomanjkanja hidroksilaze fenilalanina
Spanish	Vírus adeno-associado de serotipo HSC15 expressando la fenilalanina hidroxilase humana	Tratamiento de la deficiência de fenilalanina hidroxilase
Swedish	Adenoassocierat virus serotype HSC15 som uttrycker humant fenylalanin hydroxylas	Behandling av fenylalanin-hydroxylasebrist
Norwegian	Adenoassosiert virus serotype HSC15 som uttrykker humant fenylalanin hydroksylase	Behandling av fenylalanin hydroksylase mangel
Icelandic	Adenótengd veira af sermigerð HSC15 sem tjáir manna fenýlalanín hýdroxýlasa	Meðferð við fenýlalanín hýdroxýlasaskorti