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Committee for Orphan Medicinal Products

# Public summary of opinion on orphan designation

## Tetrahydrobiopterin for the treatment of hyperphenylalaninemia

On 8 June 2004 orphan designation (EU/3/04/199) was granted by the European Commission to Dr. Gertrud Thormann, France, for tetrahydrobiopterin for the treatment of hyperphenylalaninemia.

The sponsorship was transferred first to BioMarin Europe Ltd, Ireland, in March 2005, then to Serono Europe Limited, United Kingdom, in August 2006, then to Merck KGaA, Germany, in September 2007 and subsequently to Merck Serono Europe Limited, United Kingdom, in March 2011.

### What is hyperphenylalaninemia?

Hyperphenylalaninemia or phenylketonuria, is an inherited disease caused by a genetic abnormality which results in reduced activity of an enzyme, phenylalanine hydroxylase. This enzyme is responsible for conversion of a certain aminoacid (a building block for a protein) called phenylalanine, into another aminoacid called tyrosine. The result of this enzyme deficiency is an accumulation of high concentrations of phenylalanine in the blood and urine, up to harmful levels. Phenylalanine is toxic at high levels and can lead to severe brain damage. The disease is subdivided into mild, moderate and severe forms, according to the degree of elevation of phenylalanine blood levels.

Hyperphenylalaninemia is chronically debilitating and is characterised by mental retardation if left untreated.

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

At the time of designation, hyperphenylalaninemia affected approximately 1.7 in 10,000 people in the European Union (EU)*. This is equivalent to a total of around 64,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

*Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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## What treatments are available?

At the time of submission of the application for orphan drug designation, the treatment of hyperphenylalaninemia consisted of lifelong strict dietary protein restriction aiming to reduce phenylalanine intake.

Satisfactory argumentation has been submitted by the sponsor to justify the assumption that the medicinal product might be of potential significant benefit for the treatment of hyperphenylalaninemia, particularly in terms of improved tolerance to phenylalanine dietary intake. The assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

## How is this medicine expected to work?

Tetrahydrobiopterin might help to restore the phenylalanine hydroxylase enzyme activity. As a result more phenylalanine might be converted to tyrosine, so that patients may tolerate more phenyalamine and thus higher protein intake.

## What is the stage of development of this medicine?

At the time of the submission of the orphan drug designation application, the evaluation of the effects of tetrahydrobiopterin in experimental models and clinical trials in patients with hyperphenylalaninemia were planned.

Tetrahydrobiopterin was not marketed anywhere worldwide for treatment of hyperphenylaninemia, at the time of submission. Orphan designation of tetrahydrobiopterin was previously granted in the European Union for treatment of hyperphenylalaninemia.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 14 April 2004 recommending the granting of this designation.

Update: Tetrahydrobiopterin (Kuvan) has been authorised in the EU since 2 December 2008 for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients of 4 years of age and over with phenylketonuria (PKU) who have been shown to be responsive to such treatment.

Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.

More information on Kuvan can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

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:

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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 | Tetrahydrobiopterin | Treatment of hyperphenylalaninemia |
| Bulgarian | Тетрахидробиоптерин | Лечение на хиперфенилаланинемия |
| Czech | Tetrahydrobiopterin | Léčba hyperfenylalaninémie |
| Danish | Tetrahydrobiopterin | Behandling af hyperfenylalaninæmi |
| Dutch | Tetrahydrobiopterine | Behandeling van hyperfenylalaninemie |
| Estonian | Tetrahüdrobiopteriin | Hüperfenüülalanineemia raviks |
| Finnish | Tetrahydrobiopteriini | Hyperfenyylialaninemian hoitoon |
| French | Tétrahydrobioptérine | Traitement de l'hyperphénylalaninémie |
| German | Tetrahydrobiopterin | Behandlung von Hyperphenylalaninämie |
| Greek | Τετραϋδροβιοπτερίνη | Θεραπεία της υπερφαινυλαλανιναιμίας |
| Hungarian | Tetrahidrobiopterin | Hyperphenylalaninaemia kezelése |
| Italian | Tetraidrobiopterina | Trattamento dell'iperfenilalaninemia |
| Latvian | Tetrahidrobiopterīns | Hiperfenilalanīnēmijas ārstēšana |
| Lithuanian | Tetrahidrobiopterinas | Hiperfenilalaninemijos gydymas |
| Maltese | Tetrahydrobiopterin | Kura ta' l-iperfenilalaninimja |
| Polish | Tetrahydrobiopteryna | Leczenie hiperfenyloalaninemii |
| Portuguese | Tetrahidrobiopterina | Tratamento da hiperfenilalaninemia |
| Romanian | Tetrahidrobiopterin | Tratamentul hiperfenilalaninemiei |
| Slovak | Tetrahydrobiopterín | Liečba hyperfenylalaninémie |
| Slovenian | Tetrahidrobiopterin | Zdravljenje hiperfenilalaninemije |
| Spanish | Tetrahidrobiopterina | Tratamiento de la hiperfenilalaninemia |
| Swedish | Tetrahydrobiopterin | Behandling av hyperfenylalaninemi |
| Norwegian | Tetrahydrobiopterin | Behandling av hyperfenylalaninemi |
| Icelandic | Tetrahýdróbíopterín | Meðferð við fenýlalanínskorti |

[1] At the time of transfer of sponsorship