10 May 2017
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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-[(1R)-1-Phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine for the treatment of fragile X syndrome

On 20 April 2017, orphan designation (EU/3/17/1868) was granted by the European Commission to Sentinel Oncology Limited, United Kingdom, for N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine for the treatment of fragile X syndrome.

What is fragile X syndrome?

Fragile X syndrome is an inherited disease characterised by learning disability. Other symptoms include difficulty communicating and socialising, anxiety, hyperactivity, and repetitive and stereotyped behaviours.

The disease is caused by a defect in a gene on the X chromosome. The gene is responsible for the production of a protein called fragile X mental retardation protein (FMRP), which is necessary for the development of the brain. In patients with fragile X syndrome, the defective gene cannot produce normal levels of the FMRP protein and this leads to learning disability and other neurological symptoms. Women are normally less severely affected than men, because they have a second X chromosome that usually has a normal copy of the gene.

Fragile X syndrome is a long-term debilitating disease because of the severe behavioural problems and learning disabilities it causes.

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

At the time of designation, fragile X syndrome affected approximately 2 in 10,000 people in the European Union (EU). This was equivalent to a total of around 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).

*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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for the treatment of fragile X syndrome. Patients were given general support, such as behavioural therapy and special education, and in some cases, antidepressants, medicines for attention-deficit hyperactivity disorder and antipsychotics were used to treat the symptoms of the disease. Genetic counselling (discussion of the risks of passing on the condition to children) was recommended for families with a history of fragile X syndrome.

How is this medicine expected to work?

FMRP regulates production of certain proteins in the brain. In patients with fragile X syndrome, low levels of FMRP result in excess production of proteins, which interfere with the normal working and development of the brain.

This medicine works by blocking the action of another protein called S6K1. S6K1 stimulates protein production. By blocking the activity of S6K1, the medicine is expected to counterbalance the effects of low levels of FMRP and thus reduce production of damaging levels of proteins.

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, no clinical trials with the medicine in patients with fragile X syndrome had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for fragile X syndrome 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 15 March 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	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine	Treatment of fragile X syndrome
Bulgarian	N-[(1R)-1-фенилетил]-6-{1H-пиразоло[3,4-d]пиримидин-4-yl}квиназолин-2-амин	Лечение на синдрома на чупливата X хромозома
Croatian	N-[(1R)-1-feniletil]-6-{1H-pirazolo[3,4-d]pirimidin-4-il}kvinazolin-2-amin	Liječenje sindroma fragilnog X kromosoma
Czech	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine	Léčba syndromu fragilního X
Danish	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine	Behandling af fragilt X-syndrom
Dutch	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine	Behandeling van het fragiele-X-syndroom
Estonian	N-[(1R)-1-fenüületüül]-6-{1H-pürazool[3,4-d]pürimidiin-4-üül}quinazoliin-2-amiin	Fragiilse X sündroomi ravi
Finnish	N-[(1R)-1-fenyylietyyli]-6-{1H-pyratsolo[3,4-d]pyrimidiini-4-yl}quinatsoliini-2-amiini	Särö-X-oireyhtymän hoito
French	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amine	Traitement du syndrome de l'X fragile
German	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amin	Zur Behandlung des Fragilen-X-Syndroms
Greek	N-[(1R)-1-φαινυλεθυλ]-6-{1H-πυραζολο[3,4-d]πυριμιδινο-4-yl}κιναζολινο-2-αμινη	Θεραπεία του συνδρόμου εύθραυστο X
Hungarian	N-[(1R)-1-phenylethyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amin	A fragilis X-szindróma kezelésére
Italian	N-[(1R)-1-feniletil]-6-{1H-pirazolo[3,4-d]pyiimidin-4-yl}quinazolin-2-amina	Trattamento della sindrome dell'X fragile
Latvian	N-[(1R)-1-feniletil]-6-{1H-pirazol[3,4-d]pirimidīn-4-il}kvinazolīn-2-amīns	Trauslā X sindroma ārstēšanai
Lithuanian	N-[(1R)-1-feniletil]-6-{1H-pirazolo[3,4-d]pirimidin-4-il}kvinazolin-2-aminas	Lūžiosios X chromosomos sindromo gydymas
Maltese	N-[(1R)-1-feniletil]-6-{1H-pirażol [3,4-d]pirimidin-4-il}kwinazolin-2-ammina	Kura tas-sindrome ta' X fraġli
Polish	N-[(1R)-1-fenyloetylo]-6-{1H-pyrazolo[3,4-d]pirymidyno-4-yl}kwuinazolino-2-amina	Leczenie zespołu łamliwego chromosomu X
Portuguese	N-[(1R)-1-feniletil]-6-{1H-pirazolo[3,4-d]pirimidin-4-il}quinazolin-2-amina	Tratamento da síndrome do X frágil
Romanian	N-[(1R)-1-feniletil]-6-{1H-pirazolo[3,4-d]pirimidin-4-il}chinazolin-2-amină	Tratamentul sindromului cromozomului X fragil
Slovak	N-[(1R)-1-fenyletyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolín-2-amín	Liečba syndrómu fragilného chromozómu X

[1] At the time of designation

Language	Active ingredient	Indication
Slovenian	N-[(1R)-1-pheniletil]-6-{1H-pirazol[3,4-d]pirimidin-4-yl}kvinazolin-2-amin	Zdravljenje sindroma fragilnega kromosoma X
Spanish	N-[(1R)-1-fenilethil]-6-{1H-pirazolo[3,4-d]pirimidin-4-il}quinazolin-2-amine	Tratamiento del síndrome de X frágil
Swedish	N-[(1R)-1-fenyletyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}quinazolin-2-amin	Behandling av Fragil X-syndrom
Norwegian	N-[(1R)-1-fenyletyl]-6-{1H-pyrazolo[3,4-d]pyrimidin-4-yl}kinazolin-2-amin	Behandling av Fragilt X-syndrom
Icelandic	N-[(1R)-1-phenýlethýl]-6-{1H-prazólo[3,4-d]pýyrimídín-4-yl}quínazólín-2-amín	Meðferð við heilkenni brotgjarns X (fragile X syndrome)