10 November 2014
EMA/COMP/555975/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one for the treatment of fragile X syndrome

On 15 October 2014, orphan designation (EU/3/14/1334) was granted by the European Commission to Centre National de la Recherché Scientifique (CNRS), France, for (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one for the treatment of fragile X syndrome.

What is fragile X syndrome?

Fragile X syndrome is a genetic disease characterised by moderate to severe mental retardation. 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 the mental retardation and other neurological symptoms. Men are usually more severely affected than women as they have only one X chromosome.

Fragile X syndrome is a long-term debilitating disease because of the behavioural and mental health problems 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 102,000 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 511,100,000 (Eurostat 2014).

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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, stimulants and antipsychotics were used to treat the symptoms of the disease. Genetic counselling (discussion of the risks of passing the condition on to children) was recommended for families with a history of fragile X syndrome.

How is this medicine expected to work?

FMRP is thought to regulate the production of various proteins in nerve cells. These include proteins called 'BK channels' on the surface of nerve cells that are important for normal transmission of nerve signals. In patients with fragile X syndrome, lack of FMRP is thought to result in abnormalities in these channels that prevent them from transmitting nerve signals properly.

The medicine is expected to improve the activity of the BK channels, allowing more normal transmission of nerve signals, and thus improving the symptoms of patients with fragile X syndrome.

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 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 4 September 2014 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:

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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	(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one	Treatment of fragile X syndrome
Bulgarian	(3S)-(+)-(5-хлоро-2-метоксифенил)-1,3-дихидро-3-флуоро-6-(трифлуорометил)-2H-индол-2-он	Лечение на синдрома на чупливата X хромозома
Croatian	(3S)-(+)-(5-kloro-2-metoksifenil)-1,3-dihidro-3-fluoro-6-(trifluorometil)-2H-indol-2-on	Liječenje sindroma fragilnog X kromosoma
Czech	(3S)-(+)-(5-chlor-2-methoxy-fenyl)-1,3-dihydro-3-fluor-6-(trifluormethyl)-2H-indol-2-onu	Léčba syndromu fragilního X
Danish	(3S)-(+)-(5-chlor-2-methoxyphenyl)-1,3-dihydro-3-fluor-6-(trifluormethyl)-2H-indol-2-on	Behandling af fragilt X-syndrom
Dutch	(3S)-(+)-(5-chloor-2-methoxyfenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one	Behandeling van het fragiele-X-syndroom
Estonian	(3S)-(+)-(5-kloro-2-metoksüfenüül)-1,3-dihüdro-3-fluoro-6-(trifluorometüül)-2H-indool-2-ooni	Fragiilse X sündroomi ravi
Finnish	(3S)-(+)-(5-kloori-2-metoksifenyyli)-1,3-dihydro-3-fluori-6-(trifluorimetyyli)-2H-indol-2-oni	Särö-X-oireyhtymän hoito
French	(3S)-(+)-(5-chloro-2-méthoxyphényl)-1,3-dihydro-3-fluoro-6-(trifluorométhyl)-2h-indol-2-one	Traitement du syndrome de l'X fragile
German	(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluorine-6-(trifluoromethyl)-2h-indol-2-one	Zur Behandlung des Fragilen-X-Syndroms
Greek	(3S)-(+)-(5-χλωρο-2-μεθοξυφαινυλ)-1,3-διυδρο-3-φθορο-6-(τριφθορομεθυλ)-2H-ινδολ-2-όνη	Θεραπεία του συνδρόμου εύθραυστου X
Hungarian	(3S)-(+)-(5-klór-2-metoxi-fenil)-1,3-dihidro-3-fluor-6-(trifluor-metil)-2h-indol-2-on-	A fragilis X-szindróma kezelésére
Italian	(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-uno	Trattamento della sindrome dell'X fragile
Latvian	(3S)-(+)-(5-hlor-2-metoksifenil)-1,3-dihidro-3-fluor-6-(trifluormetil)-2H-indol-2-ons	Trauslā X sindroma ārstēšanai
Lithuanian	(3S)-(+)-(5-chlor-2-metoksi-fenil)-1,3-dihidro-3-fluoro-6-(trifluormetil)-2H-indol-2-onas	Lūžiosios X chromosomos sindromo gydymas
Maltese	(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one	Kura tas-sindrome ta' X fraġli
Polish	(3S)-(+)-(5-chloro-2-metoksyfenylo)-1,3-dihydro-3-fluoro-6-(trifluorometylo)-2H-indol-2-on	Leczenie zespołu łamliwego chromosomu X

[1] At the time of designation

Language	Active ingredient	Indication
Portuguese	(3S)-(+)-(5-cloro-2-metoxifenil)-1,3-dihidro-3-fluoro-6-(trifluorometil)-2H-indol-2-um	Tratamento da síndrome do X frágil
Romanian	(3S)-(+)-(5-cloro-2-metoxifenil)-1,3--dihidro-3-fluoro-6-(trifluoromethyl)-2H-indol-2- onă	Tratamentul sindromului cromozomului X fragil
Slovak	(3S)-(+)-(5-chlór-2-metoxy-fenyl)-1,3-dihydro-3-fluór-6-(trifluórmetyl)-2H-indol-2-ón	Liečba syndrómu fragilného chromozómu X
Slovenian	(3S)-(+)-(5-kloro-2-metoksifenil)-1,3-dihidro-3-fluoro-6-(trifluorometil)-2H-indol-2-on	Zdravljenje sindroma fragilnega kromosoma X
Spanish	(3S)-(+)-(5-chloro-2-methoxifenil)-1,3-dihidro-3-flúor-6-(trifluoromethil)-2H-indol-2-uno	Tratamiento del síndrome de X frágil
Swedish	(3S)-(+)-(5-klor-2-metoxifenyl)-1,3-dihydro-3-fluor-6-(trifluormetyl)-2H-indol-2-en	Behandling av Fragil X-syndrom
Norwegian	(3S)-(+)-(5-klor-2-metoksyfenyl)-1,3-dihydro-3-fluor-6-(trifluormetyl)-2H-indol-2-on	Behandling av Fragilt X-syndrom
Icelandic	(3S)-(+)-(5-klóró-2-metoxýfenýl)-1,3-díhýdró-3-flúór-6-(tríflúórmetýl)-2H-indól-2-ón	Meðferð við heilkenni brotgjarns X (fragile X syndrome)