

31 March 2014  
EMA/COMP/29766/2014  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl}piperidin-1-yl]methanone for the treatment of Rett syndrome

On 19 February 2014, orphan designation (EU/3/14/1242) was granted by the European Commission to Neurolix UK Ltd., United Kingdom, for 3-chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl}piperidin-1-yl]methanone for the treatment of Rett syndrome.

### What is Rett syndrome?

Rett syndrome is a genetic disease that is caused by abnormalities in the *MECP2* gene, which is important for the normal functioning of nerve cells. This gene is in the X chromosome, one of the two chromosomes (X and Y) that determine the gender. Rett syndrome almost exclusively affects girls (who have two X chromosomes) as male babies (who have only one X chromosome) with the condition do not usually survive. Although the disease is genetic, most girls affected (over 95%) do not inherit it from their parents.

Girls with Rett syndrome have severe mental retardation, which first appears between six and 18 months of age. Other symptoms include difficulty breathing, irregular heartbeat, a gradual loss of the ability to move, feeding difficulties, sleeping problems, constipation, repetitive hand movements and seizures (fits).

Rett syndrome is a seriously debilitating and life-threatening disease mainly because of problems with breathing and the heart rhythm.

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

At the time of designation, Rett syndrome affected less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 51,000 people<sup>\*</sup>, 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).

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<sup>\*</sup>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).

## **What treatments are available?**

At the time of designation, no satisfactory methods were authorised in the EU for treating Rett syndrome. Girls with the disease were given physiotherapy, speech therapy and nutritional support to help relieve the symptoms of the disease. Medicines to control seizures were also used, as well as laxatives and painkillers.

## **How is this medicine expected to work?**

Girls with Rett syndrome tend to have low levels of serotonin, a substance in the brain and spinal cord that helps maintain a normal breathing rhythm. The medicine acts at certain receptors for serotonin called 5-HT<sub>1A</sub>. By stimulating these receptors, the medicine replaces the action of some of the missing serotonin in the brain and spinal cord. This is expected to help restore normal breathing rhythm in girls with Rett syndrome.

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

The effects of this 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 Rett syndrome had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for Rett syndrome, but orphan designation of the medicine had been granted in the United States for treatment of the condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 9 January 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:

Neurolix UK Ltd.  
27 Old Gloucester St  
London WC1N 3AX  
United Kingdom  
E-mail: [anewmantancredi@neurolix.com](mailto:anewmantancredi@neurolix.com)

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<sup>1</sup>, Norwegian and Icelandic**

Language	Active ingredient	Indication
English	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Treatment of Rett syndrome
Bulgarian	3-хлоро-4-флуорофенил-[4-флуоро-4-{[(5-метилпиримидин-2-илметил) amino]метил} пиперидин-1-ил]метадон	Лечение на Синдром на Rett
Czech	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Léčba Rett-syndromu
Croatian	3-kloro-4-fluorofenil-[4-fluoro-4-{[(5-metilpirimidin-2-ilmetil) amino]metil} piperidin-1-il]metanon	Liječenje Rettovog sindroma
Danish	3-kloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanon	Behandling af Rett syndrom
Dutch	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Behandeling van het Syndroom van Rett
Estonian	3-kloor-4-fluorfenüül-[4-fluor-4-{[(5-metüülpürimidiin-2-üülmetüül) amino]metüül} piperidiin-1-üül]metanoon	Rett' sündroomi ravi
Finnish	3-kloori-4-fluorofenyyl- [4-fluoro-4-{[(5-metyylipyrimidiini-2-yyli]metyyli) amino]metyyli} piperidiini-1-yyli]metanoni	Rettin oireyhtymän hoito
French	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]méthanone	Traitement du syndrome de Rett
German	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Behandlung des Rett-Syndroms
Greek	3-Χλωρο-4-φθοροφαινυλ-[4-φθορο -4-{[(5-μεθυλπυριμιδιν-2-υλμεθυλ) αμινο]μεθυλ} πιπεριδιν-1-υλο]μεθανόνη	θεραπεία του συνδρόμου Rett
Hungarian	3-klór-4-fluorfenil[4-fluor-4-{[(5-metilpirimidin-2-ilmetil) amino]metil} piperidin-1-il]metanon	Rett szindróma kezelése
Italian	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Trattamento della sindrome di Rett
Latvian	3-hloro-4-fluorofenil-[4-fluoro-4-{[(5-metilpirimidīn-2-ilmetil) amino]metil} piperidīn-1-il]metanons	Retta sindroma terapija

<sup>1</sup> At the time of designation

Language	Active ingredient	Indication
Lithuanian	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Rett'o sindromo gydymas
Maltese	3-Chloro-4-fluorofenil-[4-fluoro-4-{[(5-metilpirimidin-2-ilmetil) amino]metil} piperidin-1-il]metanonas	Kura tas-sindrome ta' Rett
Polish	3-Chloro-4-fluorofenylo-[4-fluoro-4-{[(5-metylpirymidyn-2-ylmetylo) amino]metylo} piperydyn-1-yl]metanone	Leczenie zespołu Retta
Portuguese	3-Cloro-4-fluorofenil-[4-fluoro-4-{[(5-metilpirimidina-2-ilmetil) amino]metil} piperidina-1-il]metanone	Tratamento do síndrome de Rett
Romanian	3-Cloro-4-fluorofenil-[4-fluoro-4-{[(5-metilpirimidin-2-ilmetil) amino]metil} piperidin-1-il]metanonă	Tratamentul sindromului Rett
Slovak	3-chlóro-4-fluorofenyl-[4-fluóro-4-{[(5-metylpyrimidín-2-ylmetyl) amino]metyl} piperidín-1-yl]metanón	Liečba Rettovho syndrómu
Slovenian	3-kloro-4-fluorofenil-[4-fluoro-4-{[(5-metillpirimidin-2-ilmetil) amino]metil} piperidin-1-il]metanon	Zdravljenje Rettovega sindroma
Spanish	3-Chloro-4-fluorophenyl-[4-fluoro-4-{[(5-methylpyrimidin-2-ylmethyl) amino]methyl} piperidin-1-yl]methanone	Tratamiento del síndrome de Rett
Swedish	3-Kloro-4-fluorofenyl-[4-fluoro-4-{[(5-metylpyrimidin-2-ylmetyl) amino]metyl} piperidin-1-yl]metanon	Behandling av Rett syndrom
Norwegian	3-Kloro-4-fluorofenyl-[4-fluoro-4-{[(5-metylpyrimidin-2-ylmetyl) amino]metyl} piperidin-1-yl]metanon	Behandling av Retts syndrom
Icelandic	3-Chlóró-4-flúórófenýl-[4-flúóró-4-{[(5-metýlpýrimídín-2-ýlmetýl) amínó]metýl} píperidín-1-ýl]methanóne	Meðferð á Rett heilkenni