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Public summary of opinion on orphan designation

5-{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride for the treatment of Kabuki syndrome

On 19 November 2018, orphan designation (EU/3/18/2082) was granted by the European Commission to Takeda Pharma A/S, Denmark, for 5-{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride (also known as TAK-418) for the treatment of Kabuki syndrome.

What is Kabuki syndrome?

Kabuki syndrome, or Nikawa-Kuroki syndrome, is a disorder usually caused by changes (mutations) in certain genes important for normal development. Children with the condition may be born with malformations of various organs, including a distinctive shape of the eyes, nose and ears. They have reduced intellectual and speech development and poor control over their muscles, and may suffer from heart problems and epilepsy. Their immune system (the body's natural defences) is less effective, leading to frequent infections.

Kabuki syndrome is a long-term debilitating condition due to the effects on the nervous system and heart.

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

At the time of designation, Kabuki syndrome affected approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 52,000 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 517,400,000 (Eurostat 2018).



What treatments are available?

At the time of designation no satisfactory methods were authorised for treatment of Kabuki syndrome in the EU. Patients were managed with treatment aimed at relieving the various symptoms of the condition.

How is this medicine expected to work?

This medicine blocks the action of an enzyme called lysine-specific demethylase-1 (LSD-1), which among other actions works in the cells of the brain to regulate genes involved in learning and memory. It is expected that by blocking the action of LSD-1 the medicine will help to counteract the reduced development and function of brain cells seen in patients with Kabuki 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 Kabuki syndrome had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for Kabuki syndrome. 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 11 October 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 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.

Withdrawn

Translations of the active ingredient and indication in all official EU languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	5-{{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride	Treatment of Kabuki syndrome
Bulgarian	5-{{(1R,2R)-2-[(циклопропилметил)амино]циклопропил}}-N-(тетраhydro-2H-пиран-4-ил)тиофен-3-карбоксамид монохлорид	Лечение на синдром на Кабуки
Croatian	5-{{(1R,2R)-2-[(ciklopropilmetil)amino]ciklopropil}}-N-(tetrahidro-2H-piran-4-il)tiofen-3-karboksamid monohidroklorid	Liječenje Kabuki sindroma
Czech	5-{{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamidmonohydrochlorid	Léčba Kabuki syndromu
Danish	5-{{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride	Behandling af Kabuki-syndrom
Dutch	5-{{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}}-N-(tetrahydro-2H-pyran-4-yl)thiofeen-3-carboxamide monohydrochloride	Behandeling van kabukisyndroom
Estonian	5-{{(1R,2R)-2-[(tsüklopropüülmetüül)amino]tsüklopropüül}}-N-(tetrahydro-2H-püraan-4-üül)tiofeen-3-karboksamiid monovesinikkloriid	Kabuki sündroomi ravi
Finnish	5-{{(1R,2R)-2-[(syklopropyylimetyyli)amino]syklopropyyli}}-N-(tetrahydro-2H-pyraani-4-yyli)tiofeeni-3-karboksamidi monohydrokloridi	Kabuki-oireyhtymän hoito
French	Monochlorhydrate de 5-{{(1R,2R)-2-[(cyclopropylméthyle)amino]cyclopropyle}}-N-(tétrahydro-2H-pyranne-4-yl)thiophène-3-carboxamide	Traitement du syndrome de Kabuki
German	5-{{(1R,2R)-2-[(Cyclopropylmethyl)amino]cyclopropyl}}-N-(Tetrahydro-2H-Pyran-4-yl)Thiophen-3-Carboxamid Monohydrochlorid	Behandlung des Kabuki-Syndroms
Greek	Μονοϋδροχλωρική 5-{{(1R,2R)-2-[(κυκλοπροπουλομεθυλο)αμινο]κυκλοπροπουλο}}-N-(τετραϋδρο-2H-πυραν-4-υλο)θειοφαينو-3-καρβοξαμιδη	Θεραπεία του συνδρόμου Kabuki
Hungarian	5-{{(1R,2R)-2-[(ciklopropilmetil)amino]ciklopropil}}-N-(tetrahidro-2H-pirán-4-il)tiofén-3-karboxamid-monohidroklorid	Kabuki-syndroma kezelése
Italian	5-{{(1R,2R)-2-[(ciklopropilmetil) ammino]ciklopropil}}-N-(tetraidro-2H-piran-4-il)tiofene-3-carbossammide monocloridrato	Trattamento della sindrome di Kabuki
Latvian	5-{{(1R,2R)-2-[(ciklopropilmetil) amino] ciklopropil}}-N-(tetrahidro-2H-pirēn-4-il)tiofēn-3-karboksamīda monohidrohlōrīds	Kabuki sindroma ārstēšanai

¹ At the time of designation

Language	Active ingredient	Indication
Lithuanian	5-{{(1R,2R)-2-[(ciklopropilmetil)amino]ciklopropil}}-N-(tetrahidro-2H-piran-4-il)tiofeno-3-karboksamido monohidrochloridas	<i>Kabuki</i> sindromo gydymas
Maltese	5-{{(1R,2R)-2-[(ciklopropilmetil)amino]ciklopropil}}-N-(tetraidrat-2H-piran-4-yl)tijofen-3-monoidroklorur tal-karbossammid	Trattament tas-sindrome Kabuki
Polish	Monohydrowodorek 5-{{(1R,2R)-2-[(cyklopropylmetylo)amino]cyklopropylo}}-N-(tetrahydro-2H-pyrano-4-yl)tiofeno-3-karboksamidu	Leczenie zespołu Kabuki
Portuguese	Monocloridrato de 5-{{(1R,2R)-2-[(ciclopropilmetil)amino]ciclopropil}}-N-(tetra-hidro-2H-piran-4-il)tiofeno-3-carboxamida	Tratamento da síndrome de Kabuki
Romanian	5-{{(1R,2R)-2-[(ciclopropilmetil)amino]ciklopropil}}-N-(tetrahidro-2H-piran-4-il)tiofen-3-carboxamidă monoclorhidrat	Tratamentul sindromului Kabuki
Slovak	5-{{(1R,2R)-2-[(cyklopropylmetyl)amino]cyklopropyl}}-N-(tetrahydro-2H-pyran-4-yl)tiofén-3-karboxamid monohydrochlorid	Liečba Kabuki syndrómu
Slovenian	5-{{(1R,2R)-2-[(ciklopropilmetil)amino]ciklopropil}}-N-(tetrahidro-2H-piran-4-il)tiofen-3-karboksamid monohidroklorid	Zdravljenje kabuki sindroma
Spanish	5-{{(1R,2R)-2-[(ciclopropilmetil)amino]ciclopropilo}}-N-(tetrahidro-2H-pirano-4-yl)tiofeno-3-carboxamida monohidroclorato	Síndrome de Kabuki
Swedish	5-{{(1R,2R)-2-[(cyklopropylmetyl)amino]cyklopropyl}}-N-(tetrahydro-2H-pyran-4-yl)tiofen-3-karboxamidmonohydroklorid	Behandling av Kabukisyndrom
Norwegian	5-{{(1R,2R)-2-[(syklopropylmetyl)-amino]-syklopropyl}}-N-(tetrahydro-2H-pyran-4-yl)-tiofen-3-karboksamid-monohydroklorid	Behandling av Kabuki syndrom
Icelandic	5-{{(1R,2R)-2-[(sýklóprópýlmetýl)amínó]sýklóprópýl}}-N-(tetrahýdró-2H-pýran-4-ýl)þíófen-3-karboxamíðmónóhýdróklóríð	Meðferð við Kabuki-heilkenni