16 August 2018
EMA/395070/2018

Public summary of opinion on orphan designation

2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one for the treatment of tuberculosis

On 27 June 2018, orphan designation (EU/3/18/2029) was granted by the European Commission to Klinikum der Universität München, Germany, for 2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one (also known as BTZ-043) for the treatment of tuberculosis.

What is tuberculosis?

Tuberculosis (TB) is an infectious disease caused by bacteria called *Mycobacterium tuberculosis*. People become infected by inhaling infected droplets from the cough or sneeze of people who have the disease. TB primarily affects the lungs (called pulmonary TB) but it can also spread to other parts of the body, such as the bones or the nervous system. The symptoms of TB include persistent cough, fever, weight loss and night sweats. Not every person infected will develop the symptoms of the disease.

TB is a long-term debilitating disease that may be life threatening, mainly because of the severe damage to the lungs that does not allow the patient to breathe normally, and because the bacteria causing the disease are often resistant to existing treatments.

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

At the time of designation, TB affected approximately 1.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 83,000 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).

What treatments are available?

At the time of designation, several antibiotics were authorised in the EU to treat TB. These were used in combination and for long periods of time, normally at least six months.

[*]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).

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

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with TB. Laboratory studies indicate that it may work together with bedaquiline, which is used for drug-resistant TB. The medicine may also work better than isoniazid, which is normally used as initial treatment for TB. Finally, laboratory studies have not identified any tuberculosis bacteria with resistance to this medicine, even among strains known to be resistant to several medicines.

This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

This medicine works by blocking the action of an enzyme that the tuberculosis bacteria use to make an important component of their cell wall, which is essential for the bacteria to grow and multiply. The enzyme is called DprE1. By blocking its action, the medicine is expected to kill the bacteria or prevent them from growing and multiplying.

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 TB had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for TB. Orphan designation 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 24 May 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.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Treatment of tuberculosis
Bulgarian	2-[(2S)-2-метил-1,4-диокса-8-азаспиро[4.5]дек-8-ил]-8-нитро-6-трифлуорометил-4H-1,3-бензотиазин-4-он	Лечение на туберкулоза
Croatian	2-[(2S)-2-metill-1,4-dioksa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-on	Liječenje tuberkuloze
Czech	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Léčba tuberkulózy
Danish	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Behandling af tuberkulose
Dutch	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Behandeling van tuberculose
Estonian	2-[(2S)-2-metüül-1,4-dioksa-8-asaspiro[4.5]dec-8-üül]-8-nitro-6-trifluorometüül-4H-1,3-bensotiasiin-4-oon	Tuberkuloosi ravi
Finnish	2-[(2S)-2-metyyli-1,4-dioksa-8-atsaspiro[4.5]dek-8-yyli]-8-nitro-6-trifluorometyyli-4H-1,3-bentsotiatsiini-4-oni	Tuberkuloosin hoito
French	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Traitement de la tuberculose
German	2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one	Behandlung der Tuberkulose
Greek	2-[(2S)-2-μεθυλ-1,4-διοξα-8-αζασπιρο[4.5]δεκ-8-υλ]-8-νιτρο-6-τριφθορομεθυλ-4H-1,3-βενζοθειαζιν-4-όνη	Θεραπεία της φυματίωσης
Hungarian	2-[(2S)-2-metil-1,4-diossa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluorometil-4H-1,3-benzothiazin-4-one	Tuberculosis kezelése
Italian	2-[(2S)-2-metil-1,4-diossa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-one	Trattamento della tubercolosi
Latvian	2-[(2S)-2-metil-1,4-dioksa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazīn-4-ons	Tuberkulozes ārstēšana
Lithuanian	2-[(2S)-2-metil-1,4-dioksa-8-azaspiro[4.5]dek-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-onas	Tuberkuliozės gydymas
Maltese	2-[(2S)-2-metil-1,4-dioksa-8-ażaspiro[4.5]deċ-8-il]-8-nitro-6-trifluworometil-4H-1,3-benżotiażin-4-on	Kura tat-tuberkuloži
Polish	2-[(2S)-2-metyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluorometyl-4H-1,3-benzotiazin-4-on	Leczenie gruźlicy
Portuguese	2-[(2S)-2-metil-1,4-dioxa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-ona	Tratamento da tuberculose
Romanian	2-[(2S)-2-metil-1,4-dioxa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-onă	Tratamentul tuberculozei

[1] At the time of designation

Language	Active ingredient	Indication
Slovak	2-[(2S)-2-metyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluorometyl-4H-1,3-benzotiazín-4-ón	Liečba tuberkulózy
Slovenian	2-[(2S)-2-metil-1,4-dioksa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzotiazin-4-on	Zdravljenje tuberkuloze
Spanish	2-[(2S)-2-metil-1,4-dioxa-8-azaspiro[4.5]dec-8-il]-8-nitro-6-trifluorometil-4H-1,3-benzothiazin-4-on	Tratamiento de la tuberculosis
Swedish	2-[(2S)-2-metyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluorometyl-4H-1,3-benzothiazin-4-one	Behandling av tuberkulos
Norwegian	2-[(2S)-2-metyl-1,4-dioksa-8-azaspiro[4.5]dek-8-yl]-8-nitro-6-trifluorometyl-4H-1,3-benzotiazin-4-on	Behandling av tuberkulose
Icelandic	2-[(2S)-2-metýl-1,4-díoxa-8-azaspiro[4.5]dec-8-yl]-8-nítró-6-tríflúorometýl-4H-1,3-benzótíazín-4-on	Meðferð við berklum