31 July 2020
EMADOC-1700519818-446338
EMA/OD/0000021750
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Pretomanid FGK (pretomanid)
Treatment of tuberculosis
EU/3/07/513
Sponsor: FGK Representative Service GmbH

Note

COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	(S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine
International Non-Proprietary Name	Pretomanid
Tradename	Pretomanid FGK
Orphan condition	Treatment of tuberculosis
Sponsor's details:	FGK Representative Service GmbH Heimeranstrasse 35 Schwanthalerhoehe-Laim 80339 Munich Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Ulrich Granzer
COMP opinion date	10 October 2007
EC decision date	5 December 2007
EC registration number	EU/3/07/513
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dr Ulrich Granzer to FGK Representative Service GmbH – EC decision of 24 June 2015
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Ingrid Wang
Applicant	FGK Representative Service GmbH
Application submission date	11 March 2019
Procedure start date	28 March 2019
Procedure number	EMA/H/C/005167
Invented name	Pretomanid FGK
Proposed therapeutic indication	Pretomanid FGK is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Further information on Pretomanid FGK can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/pretomanid-fgk
CHMP opinion date	26 March 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Eva Malikova / Nikolaos Sypsas
Sponsor's report submission date	22 November 2019
COMP discussion	17-19 March 2020
COMP opinion date	27 March 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2007 designation was based on the following grounds:

- tuberculosis (hereinafter referred to as "the condition") was estimated to be affecting approximately 2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to pulmonary and extrapulmonary disease;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine may be of significant benefit to those affected by the condition;

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor has not indicated any scientific changes to the understanding of tuberculosis as a condition. Tuberculosis (TB) is an infectious disease usually caused by Mycobacterium tuberculosis (MTB) bacteria. Tuberculosis generally affects the lungs but can also affect other parts of the body. Most infections do not have symptoms, in which case it is known as latent tuberculosis.

Drug resistant tuberculosis (including multi drug resistant (MDR)TB and extensively drug resistant (XDR)TB) are subsets of tuberculosis and are seen as particularly debilitating and have been previously identified as areas of unmet medical need.

There is an array of ICD-10 codes for tuberculosis depending on organ of involvement and type of diagnostic test (A15-A19).

The proposed therapeutic indication "Pretomanid FGK is indicated as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)." falls within the scope of the designated orphan condition "Treatment of tuberculosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the CHMP through the assessment of the positive benefit/risk balance. Please refer to the EPAR for details.

Chronically debilitating and/or life-threatening nature

Tuberculosis in general and specifically drug-resistant TB is still a life-threatening disease, in particular for people with an impaired immune system (such as HIV patients). In the EU in 2017 the total number of fatal TB cases was 4,125 (WHO 2018). Even though the number is small in comparison to the total EU population it represents as much as 8% of all TB patients in the EU (4,125 / 49,494), with individual rates in the member states in the range 4% - 15% (WHO 2018).

Since initial designation three new medicinal products have been authorized for the treatment of (multidrug) resistant tuberculosis: bedaquiline (Sirturo), delamanid (Deltyba), and para-aminosalicylic acid (Granupas). None of these products are explicitly authorized for the management of XDR-TB. The mortality data presented above have been collected during a period when these agents were already authorized in the EU indicating that despite their availability TB has still to be considered being a life-threatening disease.

Number of people affected or at risk

The sponsor based the prevalence calculation on the WHO registry of TB patients in Europe. The sponsor calculated the prevalence with and without the UK inclusion. At the time of this review, Brexit negotiations were not yet finalised and it was considered more appropriate to include the UK in the overall calculation. However, the incidence of TB in the UK is lower than some other EU states and so the exclusion of the UK does not impact on the overall prevalence in the EU. The sponsor commented also on the reduced annual incidence of TB in the recent years.

The estimated prevalence of tuberculosis in the EU is 1.1 per 10,000 with or without the UK, which is substantially less than the estimated prevalence of 2 at the time of the initial designation. In consequence, the prevalence of TB in the EU is still below the orphan threshold of 5 per 10,000 in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

WHO has published several treatment guidelines for the management of TB (WHO 2019; WHO 2017, WHO 2014). In general, the pharmacotherapy of TB depends on (a) its resistance pattern and (b) the clinical form of tuberculosis. Due to the pronounced threat of development of drug resistance combination treatments of several substances are always administered.

Authorised treatments include: Isoniazid, Rifampicin, Rifabutin, Delamanid, Bedaquiline, Ethambutol, Capreomycin, Streptomycin, Cycloserine, Pyrazinamide, Para-aminosalicylic acid, a combination of Isoniazid and rifampicin; a combination of Isoniazid, rifampicin and pyrazinamide; and a combination of Isoniazid, rifampicin, pyrazinamide and ethambutol hydrochloride.

Significant benefit

In the Nix-TB study the efficacy was demonstrated in patients with pulmonary XDR- and treatment intolerant/non-responsive (TI/NR) MDR-TB. As described the overall outcome was favourable for 90%

of patients compared to 65% in a matched control cohort receiving bedaquiline and linezolid in combination with a median of 6 other medicines. In addition, tuberculosis symptoms generally improved over the treatment period. This included at end of treatment no coughing reported for 70% of subjects (compared to 22% at baseline), no chest pain for 89% (versus 59% at baseline), no shortness of breath for 90% (versus 53% at baseline) and no tiredness/weakness for 92% (compared to 49% at baseline).

Notably, in the Nix-TB trial patients were treated for 6 months with three oral medicines, whereas the patients in the control cohort received treatment over a median time of 16.5 months with a median of 8 medications (bedaquiline, linezolid (in 82% of patients) plus six other medicines). This is considered of relevance since the long treatment time is known to be a burden for patients.

The study population on enrolment consisted of patients with XDR-TB (65% = 71/109) or MDR-TB that were not responsive or intolerant to treatment (35% = 38/109). In consequence, all patients had TB that was resistant to isoniazid and rifampicin. Significant benefit over these two agents (including fixed combinations that are based on these two agents: Rimstar, Rimfater/Rimcure, Rifinah/Rimactazid) is based on improved efficacy since 90% of the enrolled patients responded to treatment with the pretomanid based BPaL regimen (89% XDR-TB and 92% TI/NR-MDR-TB). This also includes rifabutin since a high degree of cross-resistance between rifabutin and rifapentine is well known (WHO 2014).

In addition, the vast majority of patients (96% = 105/109) was treated with other anti-tuberculosis agents at the time of enrolment. Frequently used prior TB medication comprise in particular:

- Pyrizinamide: 94% (103/109)
- Terizidone: 92% (100/109)
- Para-aminosalicylic acid/para-aminosalicylate sodium: 74% (81/109)
- Ethambutol: 65% (71/109)

Of note, terizidone is not authorized in the EU. Terizidone is a prodrug of cycloserine.

Pretomanid will be administered in combination with bedaquiline (and linezolid that is formally not authorized for the management of TB in the EU). Hence, the Nix-TB study demonstrates improved efficacy of Pretomanid by using it on top of a bedaquiline regimen.

The sponsor also discussed significant benefit over delamanid ("Deltyba"), which is authorised for MDR-TB and therefore also formally encompasses the XDR-TB population. The proposed indication overlaps with the indication of delamanid, however the evidence of efficacy of delamanid in XDR-TB is minimal. The evidence that exists indicates that the efficacy of delamanid is less pronounced in XDR-TB than in MDR-TB. For example, in the Phase 2 study 242-07-204 no significant reduction in time to sputum culture conversion (SCC) over 6 months in the primary analysis was observed (delamanid group: 51 days versus placebo group: 57 days; hazard ratio 1.17 (95% CI: 0.91-1.51; p=0.2157). In addition, no clinically meaningful or statistically significant differences were observed in terms of cure or mortality. Specifically, the study included not more than 12 patients (3.7%) with XDR-TB. The only efficacy information published on this subgroup is considerably slower median time to SCC of 113 days (von Groote-Bidlingmaier et al. 2019). Since the XDR-TB populations treated in both studies, Nix-TB and 242-07-204, were comparable in terms of resistance pattern, the COMP also concluded on significant benefit of pretomanid over this product based on improved efficacy.

Overall, in line with the CHMP assessment, the COMP considered that the assumption of significant benefit of Pretomanid over the standard of care has been confirmed for the proposed target population

based on the observed improved efficacy. The considerations of the shorter treatment period and less complex treatment combination contribute to the overall perception of benefit. However, the translation of these improvement to the clinical benefit of the patient would have to be measured on validated patient reported outcome scales to be considered as major contribution to patient care.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 27 March 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of tuberculosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and associated with 8% mortality rate. The condition is also chronically debilitating due to pulmonary and extrapulmonary disease;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Pretomanid FGK may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor presented data from the pivotal study demonstrating improved efficacy of Pretomanid FGK used in combination with bedaquiline and linezolid over standard of care regimens. The indirect comparison to the standard of care in patients with extensively drug resistant or multi-drug resistant tuberculosis showed increased proportion of favourable outcomes with the use of the combination treatment containing Pretomanid FGK. The Committee considered this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Pretomanid FGK, (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine, pretomanid for treatment of tuberculosis (EU/3/07/513) is not removed from the Community Register of Orphan Medicinal Products.