Pretomanid

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

Codes ATC: J04AK08

Indication	Multi-drug resistant Mycobacterium tuberculosis Code ICD11: ML32.00
INN	Pretomanid
Type de médicament	Chemical agent
Type de liste	Liste complémentaire
Formulations	Oral > Solid > tablet: 200 mg
Historique des statuts LME	Ajouté pour la première fois en 2023 (TRS 1049)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org ↗ Lire la suite sur les brevets. ↗
Wikipédia	Pretomanid ↗
DrugBank	Pretomanid ↗

Recommandation du comité d'experts

The Expert Committee noted that tuberculosis, including drug-resistant tuberculosis, remains a significant public health threat and is responsible for considerable morbidity and mortality. The Committee also noted that treatment for drug-resistant tuberculosis often carries a high pill-burden over a long treatment duration, and that non-compliance with treatment is common, leading to unfavourable outcomes for both individuals and the community. High rates of non-adherence to standard treatment regimens for MDR-TB are common, which often result in unfavourable outcomes, emergence of further drug resistance, continued spread of disease and increased mortality. The introduction of the BPaLM and BPaL regimens provides efficacious, safe, well tolerated treatment options that have shortened overall treatment duration and improved compliance and favourable outcomes. The Committee considered that the available evidence from clinical trials supports the efficacy and safety of pretomanid, as part of the BPaLM and BPaL regimens, and noted experiences reported from countries where these regimens have been introduced in tuberculosis treatment programmes. The Committee also noted that the BPaL and BPaLM regimens have a shorter overall treatment duration compared with alternative regimens, which may contribute to improved treatment adherence and more favourable outcomes. The Committee noted that use of the BPaLM and BPaL regimens is recommended in current WHO guidelines for treatment of MDR-TB. Based on these considerations, the Committee therefore recommended the inclusion of pretomanid on the complementary list of the EML for use as part of a combination regimen with bedaquiline and linezolid with or without moxifloxacin for the treatment of multidrug-resistant or rifampicin-resistant tuberculosis in patients aged 14 years and older.

Contexte

Pretomanid has not previously been evaluated for inclusion on the EML. Bedaquiline, linezolid and moxifloxacin are currently included for treatment of multidrug- and rifampicin-resistant tuberculosis. These medicines are used in combination in the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) and bedaquiline, pretomanid, linezolid (BPaL) regimens. Treatment

duration is 26 weeks. The BPaL regimen may be extended to 9 months (39 weeks) if necessary.

Pertinence pour la santé publique

In 2021, an estimated 10.6 million people fell ill with tuberculosis worldwide, and there were 1.6 million deaths. Also in 2021, an estimated 450 000 new cases of rifampicin-resistant tuberculosis occurred. In 2019, tuberculosis was the 13th leading cause of death. Multidrug-resistant tuberculosis (MDR-TB) remains a public health crisis and a health security threat. Only about one in three people with drug-resistant tuberculosis accessed treatment in 2020 (1). Existing drug-resistant tuberculosis treatment regimens often include five to seven medicines and more than 14000 pills taken over a duration of up to 18 months or sometimes longer. High rates of non-adherence are common, which often result in unfavourable outcomes, emergence of drug resistance, continued spread of the disease and increased mortality. The introduction of the BPaLM and BPaL regimens provides efficacious, safe, well tolerated treatment options that have shortened overall treatment duration and improved compliance and favourable outcomes.

Bénéfices

The Nix-TB study was an open-label, single-arm study conducted at three South African sites, investigating treatment with (BPaL in patients with highly drug-resistant pulmonary tuberculosis (2). The primary endpoint was the incidence of an unfavourable outcome, defined as treatment failure (bacteriological or clinical) or relapse, through 6-months follow-up after the end of treatment. Participants were classified as having a favourable outcome at 6 months after the end of treatment if they had resolution of clinical disease, a negative culture status, and had not already been classified as having had an unfavourable outcome. Other efficacy endpoints and safety were also evaluated. The study enrolled 109 participants, and 107 participants were included in the modified intent-to-treat population for evaluation of efficacy. Six months after the end of treatment, nine (8%) participants had an unfavourable outcome and 98 (92%) had a favourable outcome (95% confidence interval (CI) 84.6% to 96.0%). Of the nine participants with unfavourable outcomes, six died during treatment, one withdrew (not for treatment failure) during treatment and two relapsed during follow-up. The ZeNix study was a randomized controlled, partially-blinded, multicentre, phase III trial to evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid in 181 patients with pulmonary extensively drug-resistant tuberculosis, pre-extensively drug-resistant tuberculosis, or treatment intolerant or non-responsive MDR-TB (3). Patients were randomized to receive various doses and durations of linezolid (1200 mg or 600 mg daily; 26 weeks or 9 weeks) plus bedaquiline and pretomanid for 26 weeks. The primary endpoint was the incidence of bacteriological failure or relapse or clinical failure 6 months after the end of treatment. Other efficacy endpoints and safety were also evaluated. The modified intent-to-treat population was used for the primary efficacy analysis and included 178 participants. Among participants who received BPaL with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91% and 84%, respectively, had a favourable outcome 6 months after the end of treatment. Six of the seven unfavourable microbiological outcomes up to 78 weeks after the end of treatment occurred in participants assigned to the 9-week linezolid groups. The 1200 mg linezolid 26-week group had the highest percentage of participants who required linezolid dose modifications. The overall risk–benefit ratio favoured the group that received BPaL with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer modifications to the linezolid dose. The TB-PRACTECAL study was a randomized, open-label, phase II/III study evaluating the safety and efficacy of regimens containing bedaquiline and pretomanid in combination with existing and repurposed drugs for the treatment of pulmonary MDR-TB (4). The study was conducted in Belarus, South Africa and Uzbekistan, and enrolled participants 15 years and older. In the first stage, equivalent to a phase IIB study, participants were randomly assigned to one of four regimens. The three investigational regimens included oral bedaquiline, pretomanid and linezolid. Additionally, two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2). Treatment was administered for 24 weeks in the investigational arms. The phase III stage evaluated the treatment regimen of BPaLM compared with the local standard of care at the participating sites. The primary efficacy outcome was a composite endpoint of the percentage of unfavourable outcomes at 72 weeks after randomization. The secondary outcomes included safety outcomes and the percentage of grade 3 or 4 and serious adverse events in the investigational regimens compared with the standard of care. Enrolment was terminated based on a Data Safety Monitoring Board interim analysis of available data through week 72, which demonstrated that the BPaLM arm was significantly outperforming the standard of care arm in the percentage of unfavourable outcomes. Safety outcomes also favoured the BPaLM arm in this analysis (5). The United States Centers for Disease Control and Prevention (CDC) analysed data submitted by health departments and clinicians on patients with tuberculosis in the US who began treatment with BPaL between August 2019 and September 2020. At follow up 12 months after treatment with BPaL was started,

19/20 (95%) patients had completed treatment, and there had been no treatment failures, recurrences or deaths (6). Positive country experiences from Kyrgyzstan, South Africa and Ukraine with implementing the BPaL regimen under operational research conditions were reported at the Union World Conference on Lung Health in 2022 (unpublished).

Torts

As of May 2022, 2550 participants have been exposed to pretomanid across pretomanid clinical studies. The application described adverse events associated with the BPaL and BPaLM regimens from the Nix-TB, ZeNix and TB-PRACTECAL studies. In the Nix-TB study, participants received the BPaL regimen with linezolid dosed at 1200 mg daily for 26 weeks. At least one treatment-emergent adverse event was reported by all 109 participants. In total, 50 (46%) participants interrupted linezolid due to an adverse event and resumed at the same or lower dose, and 30 participants (28%) permanently discontinued linezolid due to an adverse event. The most common adverse events were peripheral neuropathy (81%), myelosuppression (48%), optic neuropathy (13%), cardiac rhythm disturbances (11%) and myalgia (10%). Most peripheral neuropathy events were mild to moderate and were managed through linezolid dose adjustments. Twelve (11%) participants had transaminase increases > 3 times the upper limit of normal – 12 had an alanine aminotransferase elevation and 11 participants had an aspartate aminotransferase elevation. Two of these participants had alanine and aspartate aminotransferase elevations of > 3 times the upper limit of normal as well as direct and total bilirubin elevations of > 2 times the upper limit of normal. In both cases, the study drug regimen was interrupted. In total, eight participants had their regimen interrupted for hepatic adverse events, but all resumed and completed the full 26 weeks of treatment. The maximum mean increase in the QT interval by the Fridericia method was 10 ms at week 16; no participant had a QT interval > 480 ms (2). During the ZeNix study, participants received the BPaL regimen for 26 weeks with linezolid dosed at 1200 mg or 600 mg daily for 26 weeks or 9 weeks. Treatment emergent adverse events were reported in 156 of 181 participants (86.2%), with the overall percentages comparable across treatment groups. One participant (0.6%) died due to a treatment-emergent adverse event (in the 1200 mg linezolid 9-week group), but this event was deemed not to be related to the study drug. The linezolid dose was modified (interrupted, reduced or discontinued) in 51%, 30%, 13%, and 13% of participants who received linezolid 1200 mg for 26 weeks, 1200 mg for 9 weeks, 600 mg for 26 weeks and 600 mg for 9 weeks, respectively. Adverse effects associated with linezolid include peripheral neuropathy, optic neuropathy and myelosuppression. For participants who received linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, peripheral neuropathy occurred in 38%, 24%, 24% and 13% of participants, respectively, and myelosuppression occurred in 29%, 15%, 13% and 16% of participants, respectively. Optic neuropathy developed in four (9%) participants who received linezolid at a dose of 1200 mg for 26 weeks; all the cases resolved. Optic neuropathy was not reported by participants in any other treatment groups (3). Data from TB-PRACTECAL were shared with WHO to inform the updated treatment guideline recommendations. Interim results showed that the BPaLM regimen had favourable efficacy and safety when compared with the regimens given in the control arm. The CDC analysed data submitted by health departments and clinicians on 20 patients with tuberculosis in the US who began treatment with BPaL between August 2019 and September 2020. At follow-up 12 months after treatment with BPaL was started, 19 (95%) patients had completed treatment. With regard to side-effects, 12 (60%) patients reported at least one side-effect during treatment (with the combination regimen or another medication). Side-effects included peripheral neuropathy (six patients), depression (five patients), vestibular dysfunction (three patients), vision changes (three patients), nausea (two patients) and hearing loss (two patients). The timing of side-effects could not be correlated to a specific antituberculosis drug. At the time treatment began, therapy with linezolid was initiated in 18 (90%) patients at a dose lower than the 1200 mg daily approved by the United States Food and Drug Administration (most received 600 mg daily), and in 18 patients (90%), measurement of linezolid levels was used to attain therapeutic levels while minimizing toxic effects (6). Testicular toxicity was observed in male mice and rats in all repeat-dose studies but was not observed in male monkeys in any repeat-dose study. New data on the safety of pretomanid based on hormone evaluations in four clinical studies and a paternity survey were assessed by the WHO Guideline Development Group in early 2022. These data have largely alleviated previous concerns on reproductive toxicity observed in animal studies, suggesting that adverse effects on human male fertility are unlikely. Four studies with exposure to pretomanid ranging from 2 to 6 months provided an assessment of serum hormone levels relevant to male reproductive health, including follicle-stimulating hormone, luteinizing hormone, inhibin B and testosterone (7). These hormone assessments demonstrated an improvement in the underlying hypogonadism, as reflected by increases in the testosterone and inhibin B levels in all treatment arms, which is consistent with improvements in the underlying disease state. In addition, a search for adverse events associated with fertility disorders across the 19 studies in the pretomanid clinical development programme identified no events in any male participant and one event in a female participant (irregular menstruation). None of the changes observed suggested testicular damage.

Rapport coût/efficacité

Based on current costs reported in the Global Drug Facility catalogue, for patients with body weight of 40–70 kg, drug costs for treatment with BPaLM and BPaL regimens for 26 weeks is US$ 725 and US$ 720, respectively. In comparison, MDR-TB regimens of 9–11 months would cost between US$ 564 and US$ 639. The costs of medicines for longer regimens vary by patient and country and would be between US$ 875 and US$ 942. Drug costs are only one part of the total cost of treatment and non-drug costs of delivering care and managing patients are significant. The lowest published total cost of administering shorter, 9-month MDR-TB regimens in India, which accounts for about 30% of all MDR-TB patients treated, is at least US$ 2600, while treatment with longer regimens lasting up to 18 months is US$ 5500. Comparable costs in South Africa are US$ 4700 and US$ 8400, respectively. Due to volume driven cost economies, costs in India are lower; costs are likely to be higher in other middle- or high-income countries, especially those with a relatively lower burden of disease (9). While the BPaLM and BPaL regimens are similar in drug cost compared with 9- to 11 month regimens, the difference in cost–effectiveness becomes apparent when the total cost of treatment is considered. A study found that the BPaLM and BPaL regimens would save about 40% over the cost of 9- to 11-month MDR-TB regimens (US$ 1000–2000 saving per patient) and about 75% compared with longer regimens (US$ 4000–6000 saving per patient) (9,10). Similarly, the estimated savings associated with using BPaL for pre-extensively drug-resistant tuberculosis would range between 80% and 90% (up to US$ 12 000 per patient) (10–12). These studies considered only the cost of drugs and cost of care and estimated that global savings could reach US$ 740 million annually if all patients were to, hypothetically, transition to BPaLM or BPaL regimens immediately. If patient costs are added, the savings from implementation of BPaLM and BPaL will be larger. Two additional studies investigated the comparative cost of introducing pretomanid as part of the BPaL regimen to treat drug-resistant tuberculosis versus the standard treatment across six countries. All analyses in all countries estimated that the introduction of BPaL would lead to cost savings (11,12).

Directives de l'OMS

Based on data from the TB-PRACTECAL and ZeNix studies, the 2022 WHO consolidated guidelines on tuberculosis suggest the use of a 6-month BPaLM treatment regimen (bedaquiline, pretomanid, linezolid 600 mg and moxifloxacin) rather than the standard 9- or 18-month regimens for patients with MDR-TB/rifampicin-resistant TB (conditional recommendation, very low certainty of evidence) (8). The BPaL regimen may be used in cases of documented resistance to fluoroquinolones. Pretomanid should be administered in combination with bedaquiline and linezolid, with or without moxifloxacin, as follows: • Pretomanid 200 mg orally (1 tablet of 200 mg), once daily, for 26 weeks. • Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg three times a week, with at least 48 hours between doses for 24 weeks, for a total of 26 weeks of treatment. Alternatively, bedaquiline 200 mg orally once daily for 8 weeks followed by 100 mg once daily for 18 weeks, for a total of 26 weeks of treatment. • Linezolid 600 mg orally once daily for 26 weeks with potential for dose reduction depending on tolerance. • Moxifloxacin 400 mg orally once daily for 26 weeks in patients without baseline resistance to fluoroquinolones. Treatment with the BPaL combination may be extended to 39 weeks if necessary.

Disponibilité

Pretomanid 200 mg tablets, manufactured by Viatris, have regulatory approval in the United States, European Economic Area countries and a further 20 countries globally. Pretomanid 200 mg tablets, manufactured by Mylan Laboratories, were prequalified by WHO in November 2020. Additional manufacturers are reported to have applied or plan to apply for marketing authorization in China and India.

Autres considérations

The WHO Global Tuberculosis Programme department reviewed and provided comments on the application. The proposed inclusion of pretomanid for treatment of drug-resistant tuberculosis on the EML is supported by the technical department, to be used as a component of a 6-month regimen composed of bedaquiline, pretomanid and linezolid, with or without moxifloxacin.

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