Content of this Plain Language Summary

The objective of the Plain Language Summary is to help the general public understand EUnetHTA assessments. You can find the link to the full assessment report later in the summary.

What is included in this Plain Language Summary? First, this document explains what EUnetHTA is and what this network does. Second, you will find the summary of the assessment.

What is EUnetHTA?

EUnetHTA is the European Network for Health Technology Assessment (HTA). EUnetHTA was established to create an effective and sustainable network for HTA across Europe. Our partners work together to help develop information to contribute to HTA in European countries. For more information on our goals and how we work, please visit our website and our patient flyer.

EUnetHTA consists of over 80 partners that are all non-profit organisations. All partner organisations either produce or support the production of HTA reports. For more information on HTA, visit EUnetHTA's Frequently Asked Questions.

EUnetHTA does not give any advice on reimbursement of a specific health technology. The reimbursement decision is a national or regional decision. This means that reimbursement of health technologies can also differ between countries in Europe.

What does EUnetHTA do?

EUnetHTA supports national and regional research institutions and health ministries in their decision-making. For this task, EUnetHTA uses specific methods to assess health technologies. Health technologies that may be assessed by EUnetHTA include medicines and other health technologies such as specialist medical care, surgical interventions and diagnostic tests. The purpose of this plain language summary is to help the general public understand the findings from this assessment.

Summary of the assessment

This section provides a summary of the assessment, which was published on 19/08/2020. To get a better understanding of commonly used HTA concepts, we advise you to look at this guide for words used in health technology assessment and this fact sheet.

Why did we conduct this assessment?

The purpose of this EUnetHTA assessment is to give national healthcare systems robust information about the therapy under assessment.

What is the context of this assessment?

Tuberculosis (TB) is a disease caused by germs (Mycobacterium tuberculosis) that are spread through the air from person to person. It typically affects the lungs, but can also affect other organs. Patients with TB can die without treatment. In 2019, the World Health Organization (WHO) estimated that 10 million individuals developed active TB and 1.6 million died from this disease.

While drug-susceptible TB is curable, drug-resistant TB is not more difficult to treat. This assessment focusses on two types of drug resistant tuberculosis[1]:

- Multidrug-resistant TB: the bacteria that are causing TB are resistant to drugs which are standard-of-care treatment in the first line of therapy;
- Extensively drug-resistant TB: with its additional resistance to any fluoroquinolone and at least one second-line injectable drugs.

Pretomanid is a new drug taken by mouth to treat Mycobacteria infections. In Europe, pretomanid was granted a licence in March 2020 in combination with bedaquiline and linezolid, for the treatment of adults with pulmonary, lung like, extensively drug-resistant TB or multidrug-resistant TB.

What did EUnetHTA review?

Through this assessment, EUnetHTA reviewed how well the drug combination of pretomanid with bedaquiline and linezolid worked and how safe it is in drug-resistant TB. This is compared to what is currently used to treat drug-resistant TB.

What is the drug under review?	Pretomanid in combination with bedaquiline and linezolid
What is the study group?	Adults with lunglike extensively drug-resistant TB or treatment-intolerant or nonresponsive multidrug-resistant TB
What is the drug compared to?	➢ Treatments approved for multidrug-resistant TB: • Bedaquiline • Delamanid • p-Aminosalicylic acid ➢ Other treatments not approved for multidrug-resistant TB but recommended for use by the WHO.
What are the outcomes this review investigates?	Outcomes on effectiveness of pretomanid: • Negative test for Mycobacterium TB • Cure • Treatment failure • Treatment completion

[1] https://tbfacts.org/drug-resistant-tb/

- Treatment success
- Health-related quality of life.

Outcomes on safety of pretomanid:

Adverse events, i.e., any negative medical occurrences that happen during treatment. In particular, adverse events that are:

- Fatal
- Serious adverse events, for example: pneumonia (lung infection), pulmonary TB, sepsis (bacterial infection) and anaemia (decreased red cells in the blood)
- Treatment-related adverse events, for example: peripheral neuropathy (damage to the nervous system), anaemia (decreased red cells in the blood), nausea and vomiting

What are the main findings?

Systematic search of this topic resulted in a single, still ongoing study conducted in South Africa: Nix-TB study. This assessment was based on data from this trial collected by 29th March 2019. The final results of Nix-TB trial are expected in 2021. This will be after a follow-up period of 24 months, after the end of treatment for all participants.

A total of 109 adults were included in Nix-TB to receive the BPal regimen for 6 months. The BPal regimen comprised of bedaquiline, pretomanid and linezolid,. People included had a median age of 35 years (range from 17 to 60 years) and 52.3% of them were male. Approximately half of the participants were HIV-positive (51.4%). A total of 105/109 participants (96.3%) received at least one prior medication for TB treatment, with a total number of treatments ranging from 3 to 13. Their current diagnosis was *Extensively drug-resistant TB* for 65.1% of the participants and *Treatment-intolerant/Nonresponsive Multidrug-resistant TB* 34.9% for the rest of them.

Results from Nix-TB study did show several limitations. For example, there were no long-term evidence of efficacy since the study is still ongoing. Also, there is no direct evidence for comparison with the current standard of care. Therefore, the assessment team beliefs that the true therapeutic effect of pretomanid on the outcomes relevant for this review cannot be demonstrated based on this study.

However, the Nix-TB study did provide some interesting results:

- For 98/107 individuals (92%), no treatment failure up to 6 months after the end of the treatment occurred. For the other 9 individuals (8%) it did.
- Relapse or reinfection at 24 months after the end of the treatment was assessed for only 44 participants who have completed the 24-month follow-up visit. One of them experienced a reinfection 15 months after the end of the treatment.
- From the start to the end of the treatment, the number of participants with negative test for Mycobacterium TB increased. At the end of the treatment, all living participants showed negative test results. This means that no one had active TB anymore.
- Every participant included in the Nix-TB study experienced at least one treatment-related adverse event, mainly damage to the nervous system and decreased number of red blood cells. .
- Serious adverse events were reported for 19/109 participants (17%). A total of eight deaths were reported in the study, of which six occurred during the treatment period and two during the follow-up period.

Did EUnetHTA involve stakeholders?

EUnetHTA values involvement of stakeholders in the assessments. This ensures the assessments consider/include patients' experiences and improves applicability of the assessments.

The president of the French patient organisation ACTUME, who has TB, was interviewed. Through this interview information was collected on quality of life and the current standard of care from a patient perspective. He highlighted that people expect new therapies to help treatment adherence and completion. This includes having treatments that are well tolerated, ideally for shorter durations, and easier to take (e.g., with as small a number of tablets to be taken as possible).

Additional information

This report was written by HTA organisations from France (HAS) and Croatia (MiZ). Organizations from Ukraine (MoH), the Netherlands (University of Utrecht), Spain (AEMPS) and Switzerland (SNHTA) have contributed in reviewing roles.

The full scientific content is reported in EUnetHTA assessment PTJA14, and can be found here. EUnetHTA has received funding from the European Union's Health Programme (2014-2020). The content of this summary reflects the views of the authoring team. This cannot be considered to reflect the views of the entire EUnetHTA or any body of the European Union. Individuals involved in this assessment were cleared for any potential conflict of interests.

If you have further questions, please contact: eunethta@zinl.nl