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Treatment Action Group

GLOBAL TB COMMUNITY ADVISORY BOARD

Information note
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Medical and Research Questions on the BPaL regimen and pretomanid

In August 2019, the US Food and Drug Administration (FDA) approved a new TB drug, pretomanid, for use in combination with bedaquiline and high-dose linezolid; this regimen, referred to as the BPaL regimen, is given for 6 months (extendable to 9 months) to treat adults with pulmonary extremely drug resistant TB (XDR-TB), or treatment-intolerant or non-responsive multidrug resistant TB (MDR-TB).

The FDA approval of BPaL is based on interim promising results from the Nix-TB trial: 72, or 90% of the 80 patients with at least 6 months of follow up information were reported to have a favourable treatment outcome despite high rates of side effects, notably peripheral neuropathy (experienced by 87, or 80%, of the 109 people treated in total) due to the high dose of linezolid or hepatotoxicity due to due to bedaquiline or pretomanid. These encouraging results from the Nix-TB trial are tempered against the relatively small number of patients included, the inability to compare the regimen with modern alternatives, and the lack of data for oft-forgotten groups of patients such as children, pregnant and lactating women, and people living with HIV receiving dolutegravir. The median CD4 count amongst HIV co-infected people in the Nix-TB trial was 400 cells/mm^3.

Once available, countries could consider BPaL use in targeted settings under close clinical monitoring or operational research conditions in order to offer patients a shorter treatment regimen for XDR-TB or resistance/intolerance to MDR-TB while simultaneously gathering experience in real-world programmatic settings. A number of clinical trials are looking at regimens with pretomanid, including in combination with lower doses of linezolid, such as TB Alliance's ZeNix trial and MSF's TB-PRACTECAL trial. TB-PRACTECAL will evaluate the safety and efficacy of 6-month regimens containing bedaquiline, pretomanid and lower doses of linezolid for the treatment of adolescents and adults with MDR- or XDR-TB (final outcomes expected early 2022).

While waiting for clinical trial results, there remain a number of questions regarding the potential future role of pretomanid, both within the BPaL regimen and as an individual drug:

- How effective is pretomanid outside of the BPaL regimen – what are pretomanid's independent contributions to the safety and efficacy of the BPaL regimen for XDR-TB or resistance/intolerance to MDR-TB;
- How does pretomanid compare to other available second line TB drugs, especially with delamanid, which is from the same class of drugs;
- How does the BPaL regimen compare to other regimens containing Group A and B drugs with or without delamanid – BPaL was compared to historical data from patients with XDR-TB treated between 2008–2012 and who did not receive bedaquiline, linezolid, or delamanid, all of which are part of the standard of care for XDR-TB patients today;
- Is BPaL effective against TB that might be resistant to bedaquiline, linezolid, or delamanid;
- How should patients that develop early toxicity to one or more of the drugs in BPaL be managed;
- Should bedaquiline, linezolid, or delamanid resistance testing be available and performed prior to starting the BPaL regimen;
- Is there cross-resistance between pretomanid and delamanid, since they are in the same drug class;
- What is the effectiveness and safety of pretomanid in children and what is the correct dosage for pediatric use – there is no pharmokinetic data in children;

- What are the results of studies that show pretomanid is safe after male fertility concerns from animal studies;
- How will the BPaL regimen perform in HIV infected patients with low CD4 counts or receiving an antiretroviral treatment regimen containing dolutegravir;
- Is the BPaL regimen safe to use in patients with underlying liver disease, and what is the recommended clinical monitoring plan for hepatotoxicity in such patients taking BPaL;
- What is the functional impact of peripheral neuropathy for people who received BPaL and developed this adverse event;
- Could other regimens (some being tested currently in clinical trials such as ZeNix, TB PRACETAL, or endTB) with a lower dose of linezolid or longer durations have similar favourable outcomes with fewer and less severe adverse events;
- What are the critical concentrations of pretomanid to inform drug susceptibility testing;
- Can the mechanisms of resistance to pretomanid be well described and have the predictive mutations been discovered;
- Can the use of the BPaL regimen be safely expanded beyond its FDA approved indication (XDR-TB or TI/NR MDR-TB) to include patients with MDR-TB;
- What is the optimal dose and duration of linezolid (in part being answered in ongoing clinical trials);
- Can the effectiveness of the BPaL regimen be improved by adding one or more additional second line TB drugs to the BPaL regimen.

We look forward to hearing from the TB Alliance with information they have to address these questions, including TBA and other's plans for further research, as needed.