Pretomanid – New orphan drug approval

- On August 14, 2019, the FDA announced the approval of TB Alliance's pretomanid, as part of a combination regimen with Sirturo® (bedaquiline) and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).
    - Approval of this indication is based on limited clinical safety and efficacy data.
    - This drug is indicated for use in a limited and specific population of patients.
    - Pretomanid is not indicated in patients with the following conditions: drug-sensitive tuberculosis, latent infection due *to Mycobacterium tuberculosis*, extra-pulmonary infection due to *Mycobacterium tuberculosis*, or MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy.
    - Safety and effectiveness of pretomanid has not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.

- According to the World Health Organization, in 2016, there were an estimated 490,000 new cases of MDR TB worldwide, with a smaller portion of cases of XDR TB.

- Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines.
    - Pretomanid was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs. This pathway was established to advance development and approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need.

- The efficacy of pretomanid was demonstrated in an open-label study enrolling 109 patients with XDR, treatment-intolerant MDR, or non-responsive MDR pulmonary TB. Patients received pretomanid, bedaquiline, and linezolid for 6 months with 24 months of follow-up.
    - Of the 107 patients assessed, outcomes were classified as success (culture negative status at 6 months post treatment) for 95 (89%) patients and failure for 12 (11%) patients.

- Warnings and precautions of pretomanid include risks associated with the combination treatment regimen, hepatotoxicity, myelosuppression, peripheral and optic neuropathy, QT prolongation, drug interactions, reproductive effects, and lactic acidosis.

- The most common adverse reactions (≥ 10%) with pretomanid use were peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea.

- The recommended dose of pretomanid is 200 mg orally once daily with food, for 26 weeks.
    - Pretomanid must be administered in combination with bedaquiline and linezolid.
    - The combination regimen of pretomanid, bedaquiline, and linezolid should be administered by directly observed therapy.
    - Bedaquiline should be dosed at 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks.
    - Linezolid should initially be given at 1,200 mg orally per day for 26 weeks.

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    - — Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary.
    - — Consult the pretomanid drug label for further dosing recommendations.

- TB Alliance plans to launch pretomanid by the end of the year. Pretomanid will be available as 200 mg tablets.