# PRETOMANID (*Mycobacterium tuberculosis* / Tuberculosis)

As a major global disease, Tuberculosis (TB) results in the death of millions each year with 250,000 of the deaths stemming from drug resistant TB which is classified as resistance to two of the first line drug treatments, rifampicin and isoniazid (World Health Organisation 2019).

Pretomanid, an antimicrobial agent has been approved for use alongisde bedaquiline and linezolid to treat adult patients with extremely drug resistant (XDR) TB and treatment-intolerant or non-responsive multidrug resistant (MDR) pulmonary TB (Keam 2019, p. 1797)

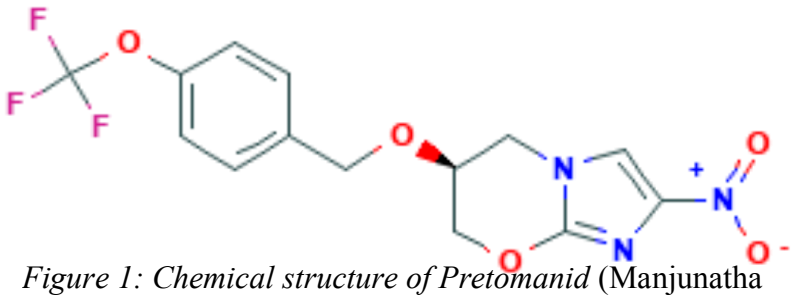


*Figure 1: Chemical structure of Pretomanid* (Manjunatha et al. 2009)

## MECHANISM OF ACTION

The prodrug pretomanid has a complex mechanism of action against both replicating and oxygen deprived non-replicating *Mycobacterium tuberculosis* bacterium (Manjunatha et al. 2009, p. 215).

Anaerobic Conditions (Non-replicating)

In the bacterium Rv3547, an enzyme called deazaflavin-dependent nitroreductase or *Ddn* that relies on reduced form of cofactor F420 metabolically activates pretomanid (Singh et al. 2008; Khambetee et al. 2018, p. 86; Drug Bank 2020). The activation of pretomanid, causes the reduction of the drug's imidazole ring resulting in three primary metabolites to be formed of which the most important is the des-nitro derivative (Heaver et al. 2015, Drug Bank 2020). The formation of this derivative results in increased levels of reactive nitrogen species such as nitric oxide within the bacilli; which ultimately leads to interference in ATP homeostasis and regular electron flow (Manjunatha et al. 2009; Denny & Palmer 2010). Thus pretomanid acts as NO donors subsequently killing *M.tuberculosis*.

Aerobic Conditions (Replicating)

Although the mechanism is currently poorly understood, it is believed that pretomanid inhibits bacterial cell wall mycolic acid biosyntehsis; killing the bacterium (Heaver et al. 2015; Drug Bank 2020). Pretomanid does this by synthesising hydroxymycolates alongside the formation of ketomycolates (Manjunatha et al. 2009, p. 215). This disrupts the formation of ketomycolates which are naturally found in the cell envelope of *M.tuberculosis* bacterium, thus inhibiting bacterial cell wall mycolic acid biosyntehsis and killing the cell (Manjunatha et al. 2009, p. 215).

## BACTERIAL RESISTANCE MECHANISMS

Pretomanid has a minimum inhibitory concentration (MIC) between 0.015-0.25 µg/ml indicating its effectiveness in acting against *M.tuberculosis* (Dookie et al. 2018). Resistance to the antimicrobial agent has been linked to mutations in the genes associated with the bioreductive activation of pretomanid within the bacterial cell (Dookie et al. 2018). These include genes associated with pro-drug activation or those involved in the cofactor biosynthetic pathway such as *Ddn* and *fbiA* respectively (Dookie et al. 2018). It can then be hypothesized that these mutations results in the inhibition of the pathway, decreasing drug activation and not producing nitrogen species, which kill the bacterium. However, studies carried out on 130 mutations in the *Fdg1* and *Ddn* genes did not appear to cause resistance to pretomanid, with Zhang and Yew (2015) obtaining a MIC value of 0.25 µg/ml.

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