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Delamanid and Pretomanid

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1. DESCRIPTION

Delamanid (Deltyba, formerly OPC-67683) and pretomanid (formerly PA-824) are two bicyclic 4-nitroimidazoles in development for treatment of tuberculosis. Delamanid was conditionally approved in Europe in 2013 and approved in Japan in 2014 for the treatment of multidrug-resistant tuberculosis (MDR-TB) in combination with an appropriate background regimen; pretomanid remains investigational-only as of this writing but is being evaluated as part of combination regimens for treatment of both drug-susceptible and MDR-TB.

Delamanid and pretomanid are bactericidal against *Mycobacterium tuberculosis* and most of the *M. tuberculosis* complex but have activity against few other mycobacteria. They are prodrugs that require activation by a mycobacterial enzyme, and their mechanisms of mycobacterial killing include both inhibition of mycolic acid synthesis and generation of toxic nitrogen radicals.

Delamanid has the chemical formula $C_{25}H_{25}F_3N_4O_6$ and molecular weight 534.48 g/mol. It is manufactured as a 50-mg film-coated tablet. Pretomanid has the chemical formula $C_{14}H_{12}F_3N_3O_5$ and molecular weight 359 g/mol. It is produced for investigational use as an oral tablet. These drugs' chemical structures are shown in Figure 139.1 (Global Alliance, 2008).

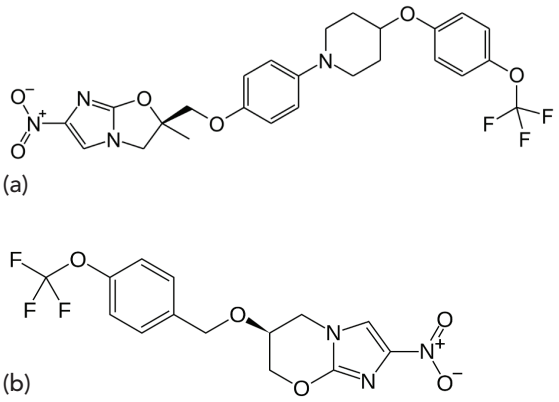

Figure 139.1. Chemical structures of (a) delamanid and (b) pretomanid.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

MYCOBACTERIUM TUBERCULOSIS COMPLEX

Delamanid and pretomanid have bactericidal activity against both replicating and hypoxic non-replicating *M. tuberculosis* (Stover *et al.*, 2000; Matsumoto *et al.*, 2006; Hurdle *et al.*, 2008). They are also active against most other members of the *M. tuberculosis* complex (European Medicines Agency, 2013), although one member of the complex, *M. canettii*, appears to be intrinsically resistant (Feuerriegel *et al.*, 2011). Delamanid has greater potency than pretomanid.

There is no known cross-resistance of delamanid and pretomanid with other tuberculosis drug classes (Matsumoto *et al.*, 2006; Stover *et al.*, 2000), and there is no antagonism between these two agents and the activity of first-line tuberculosis drugs or streptomycin (European Medicines Agency, 2013; Hurdle *et al.*, 2008). Pretomanid antagonizes the activity of bedaquiline in some regimens in a mouse model of tuberculosis (Tasneen *et al.*, 2011; Tasneen *et al.*, 2015).

NONTUBERCULOUS MYCOBACTERIA

Delamanid and, to a lesser extent, pretomanid are active against *M. kansasii*, but they are not active against most other nontuberculous mycobacteria (see Table 139.1). In particular, neither delamanid nor pretomanid have activity against mycobacteria that lack the specific nitroreductase enzyme (Ddn) that activates these prodrugs (Manjunatha *et al.*, 2006b; Dogra *et al.*, 2011).