Table 139.2. Pharmacokinetics of delamanid and pretomanid.

	Delamanid[a]	Pretomanid[b]
Bioavailability		
Oral bioavailability—adults	25–47% in the fed state	Acceptable for oral administration
Association with food	Exposure increases ~ 2.7-fold when taken with a meal and > 4 times with a fatty meal	Exposure increases in the fed state, by ~ 1.4 times for a 50-mg dose and ~ 4.5 times for a 1000-mg dose
Serum levels in relation to dosage	Less than dose proportional: a 4-fold increase in delamanid dose from 100 to 400 mg increased single-dose C_{max} by a factor of 2.4 and single-dose AUC_{∞} by a factor of 2.9	Less than dose proportional at high doses, but approximately dose proportional in the dose range 100–200 mg/day in clinical trials
Terminal $t_{½}$	30–38 hours	16–24 hours
C_{max}	0.2 μg/ml ± 0.015 μg/ml (for 100-mg twice-daily dose in fed healthy volunteers)	1.7 ± 0.3 μg/ml (for 200-mg/day dose in healthy volunteers)
AUC	2.5 μg·h/ml	30.2 ± 3.7 μg·h/ml
Drug distribution		
Apparent volume of distribution	937–16,100 liters in the terminal phase	93–167 liters after multiple doses
Protein binding	≥ 99.5% protein bound	~ 95% protein bound (measured only *in vitro*, with uncertain avidity)
Extrapulmonary sites (e.g. CNS, bone)	No data	Limited data; good CNS penetration in rats
Elimination		
Metabolism	Mostly albumin mediated in plasma, with contributions from CYP 3A4 and possibly (*in vitro* evidence) CYP1A1	Extensively metabolized via multiple routes of reductive and oxidative metabolism
Metabolites	Multiple metabolites with terminal half-lives of > 100 hours	No major metabolite in plasma
Excretion	No renal excretion	Multiple minor metabolites detected in both feces (26% of dose) and urine (65% of dose) Parent drug is not excreted in appreciable quantities
Pharmacokinetics-pharmacodynamics		
		Bactericidal activity correlates with proportion of dosing interval with free drug plasma concentrations above MIC in murine model (Ahmad *et al.*, 2011), a result consistent with plateau in early bactericidal activity of pretomanid at doses ≥ 100 mg in patients

[a]European Medicines Agency, 2014; European Medicines Agency, 2014; Sashara *et al.*, 2015.
[b]Ginsberg *et al.*, 2009b; Winter *et al.*, 2013b; Diacon *et al.*, 2010; Diacon *et al.*, 2012; Dooley *et al.*, 2014; Laurenzi *et al.*, 2007, Wang *et al.*, 2015.

contraindicated. In addition, because delamanid metabolite associated with QT prolongation (DM-6705), is formed via albumin-mediated metabolism of delamanid, and is itself metabolized by CYP3A4, albumin concentration and CYP activity are important considerations in avoiding excessive QT prolongation (European Medicines Agency, 2013).

Pretomanid, like delamanid, does not appear to inhibit or induce CYP3A4 to a clinically meaningful extent (Winter *et al.*, 2013a), but exposures to pretomanid may be affected by certain common HIV and first-line tuberculosis medications (Table 139.3). Pretomanid exposures in healthy volunteers changed minimally when co-administered with the CYP inhibitor lopinavir/ritonavir (17% AUC_{24} reduction), but were significantly reduced by co-administration with either efavirenz (35% AUC_{24} reduction) or rifampin (66% AUC_{24} reduction) (Dooley *et al.*, 2014).

6. ADVERSE REACTIONS AND TOXICITY

Clinical experience with both delamanid and pretomanid remains limited, and phase III trial results and safety profiles are not yet available for either drug. Additional safety information may emerge as they are used to treat more patients. The European Medicines Agency recommends limiting duration of delamanid use to 24 weeks, and interim World Health Organization guidance on the use of delamanid advises close treatment monitoring, pharmacovigilance, and informed patient consent (World Health Organization, 2014).