Although the long-used tuberculosis drugs isoniazid and ethionamide also inhibit mycolic acid synthesis, delamanid and pretomanid inhibit a more terminal step without evidence of isoniazid or ethionamide cross-resistance (Matsumoto *et al.*, 2006; Stover *et al.*, 2000).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Delamanid has been developed for oral administration as a 50-mg tablet. The recommended dose is 100 mg twice daily, and directly observed therapy is recommended (European Medicines Agency, 2014); a recently completed phase III clinical trial evaluated a dose of 100 mg twice daily for the first 2 months of treatment, followed by 200 mg once daily for 4 months (clinical trial NCT01424670). It should be taken with food. Delamanid should be used only in combination with an appropriate background regimen, as monotherapy of active tuberculosis is likely to result in treatment failure and acquired drug resistance.

Pretomanid is being studied in oral doses of 100 mg or 200 mg daily as part of combination regimens (Dawson *et al.*, 2015).

4b. Newborn infants and children

Safety and efficacy of delamanid in children and adolescents below 18 years has not yet been established (European Medicines Agency, 2014), but pediatric studies are under way (clinical trials NCT01856634 and NCT01859923).

Pretomanid has not yet been tested in children or adolescents.

4c. Pregnant and lactating mothers

Delamanid is not recommended in pregnant women due to lack of human safety data and some evidence of teratogenicity at maternally toxic doses in animals. Women of childbearing potential are recommended to use a reliable form of contraception while taking delamanid (European Medicines Agency, 2014). Because delamanid and metabolites are excreted in breast milk of lactating rats, and because human data are lacking, concurrent breastfeeding is also not recommended.

Pretomanid safety in pregnancy or lactation has not been determined.

4d. Those requiring altered dosages

Delamanid is not renally excreted, and no delamanid dose adjustment is needed in mild to moderate renal impairment; there are no data about removal of delamanid by hemodialysis or peritoneal dialysis. Delamanid also does not require dose adjustment in mild hepatic impairment, but use of delamanid in moderate to severe hepatic impairment is not recommended due to lack of data (European Medicines Agency, 2014). No data are available about delamanid administration in the elderly, although exposure was not age dependent in clinical trials. Use of delamanid is contraindicated in hypoalbuminemia (serum albumin < 2.8 g/dl) because of its association with QT prolongation (European Medicines Agency, 2013).

No data or recommendations for dose adjustment are reported for pretomanid.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetics and pharmacodynamics of delamanid and pretomanid are summarized in Table 139.2.

5a. Bioavailability

Oral bioavailability of both drugs is adequate for oral dosing and increases when taken with food.

5b. Drug distribution

Both drugs have large effective volumes of distribution and are highly protein bound (details in Table 139.2). Data on penetration into specific extrapulmonary sites are limited, although pretomanid appears to penetrate well into tissues, including the central nervous system in rats (Wang *et al.*, 2015).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Delamanid was initially tested and approved for twice-daily administration, but once-daily dosing is being evaluated in the continuation phase of treatment in an ongoing clinical trial. Pretomanid's bactericidal activity appears to correspond to time above MIC (Ahmad *et al.*, 2011).

5d. Metabolism and excretion

Both drugs are heavily metabolized prior to elimination, with delamanid undergoing an initial albumin-mediated metabolic step, while pretomanid follows oxidative and reductive metabolic pathways (Table 139.2).

5e. Drug interactions

Delamanid does not inhibit or induce CYP450 isoenzymes when tested at several times the steady-state C_{max} of delamanid (Matsumoto *et al.*, 2006; Shimokawa *et al.*, 2014). No interactions occur with important drug transporters (including P-gp, BCRP, AOTP1B1, OATP1B3, and OCT1), although it is noted that higher delamanid concentrations in the gut may still exert effects (European Medicines Agency, 2014).

Because of the role of CYP3A4 in delamanid metabolism, use of delamanid with strong CYP3A4 inhibitors is