day of clofazimine loading for 3 days followed by 100 mg/day clofazimine, the mean peak plasma level was 0.2 mg/l after 14 days (Diacon *et al.*, 2015)

Clofazimine is a highly lipophilic medication, and distributes primarily into fatty tissues and mononuclear phagocyte system (Cholo *et al.*, 2012). In a mouse model of tuberculosis, clofazimine accumulated in the lungs, liver, and spleen so that after 4 weeks of treatment, clofazimine levels were greater than 50 μg/g in all these tissues (Swanson *et al.*, 2015). The elimination half-life from tissues is highly variable but may be as long as 70 days (Holdiness, 1989; Reddy *et al.*, 1999). A disproportionate accumulation of clofazimine in liver and spleen after 3–8 weeks of administration was found in animal studies. Clofazimine sequesters intracellularly in these organs where it can form crystal-like drug inclusions (Baik *et al.*, 2013). In patients with leprosy, clofazimine concentration in fat tissue of up to 5.3 mg/g was found, and clofazimine concentrations > 1 mg/g were measured in bile, gallbladder, kidney, pancreas, skin, liver, spleen, lymph nodes, eyes, and lung (Mansfield, 1974). An autopsy study on a 45-year-old female on long-term high-dose clofazimine demonstrated clofazimine accumulation in spleen, pancreas, adrenal glands, liver, lung, jejunum, colon, and stomach (Jadhav *et al.*, 2004). Clofazimine crosses the blood–brain barrier poorly, and only very low levels were detected in postmortem brains (Mansfield 1974; Cholo *et al.*, 2012).

5c. Clinically important pharmacokinetic and pharmacodynamic features

There are minimal data that correlate pharmacokinetic and pharmacodynamic features of clofazimine with its clinical efficacy. In a murine study, the antituberculous activity of clofazimine did not depend on the dose administered or the tissue concentration of clofazimine. In addition, clofazimine exhibited dose-independent antituberculous bactericidal activity only 2 weeks after its commencement (Swanson *et al.*, 2015). In a human macrophage model of intracellular MAC infection, clofazimine was shown to have a prolonged postantibiotic effect even after a brief exposure to clofazimine (Horgen *et al.*, 1998). *In vitro* synergism between clofazimine and amikacin was found in 82% of *M. abscessus* and all 16 MAC isolates examined (van Ingen *et al.*, 2012).

5d. Excretion

Most clofazimine is excreted unchanged through feces via the bile, whereas both unchanged and clofazimine metabolites are found in the urine, accounting for 0.6% and 0.4% of the daily dose, respectively (Novartis Pharma, 2005; Holdiness, 1989). Small amounts of clofazimine are also found in sputum, sweat, and breast milk (Reddy *et al.*, 1999)

5e. Drug interactions

Clofazimine is a weak inhibitor of CYP3A4 and there has been a theoretical concern that clofazimine could increase the level of protease inhibitors used in HIV therapy (Cholo *et al.*, 2012; Coyne *et al.*, 2009); however, there have been no interaction studies undertaken to verify this. Clofazimine has been reported to decrease rifampicin absorption and increase the half-life and the time to reach peak serum concentration of rifampicin (Novartis Pharma, 2005), but a study of 15 patients found no effect of clofazimine on the pharmacokinetics of rifampicin (Venkatesan *et al.*, 1986) or dapsone (Pieters *et al.*, 1988). Concomitant administration of isoniazid and clofazimine results in elevated plasma and urine concentration of clofazimine, but the clinical significance of this is unclear (Novartis Pharma, 2005). Other drug interactions with estrogen and vitamin A have been reported but also are of uncertain importance (Holdiness, 1989).

6. ADVERSE REACTIONS AND TOXICITY

Generally clofazimine-related side effects (Table 137.1) are dose related and result from its long half-life and tendency to crystallize in fatty tissue and in the reticuloendothelial system. They are therefore usually slowly reversible upon discontinuation of medication (Cholo *et al.*, 2012; Novartis Pharma, 2005). More water-soluble riminophenazine analogs that are less likely to accumulate than clofazimine have shown equivalent and sometimes superior efficacy but remain in preclinical development (Lu *et al.*, 2011).

6a. Dermatological adverse effects

Dermatological adverse effects are common with clofazimine. Reddish-black or orange skin discoloration occurs in 75–100% of patients within a few weeks of commencement of clofazimine (Moore, 1983; Reddy *et al.*, 1999). Discoloration can also occur in hair, urine, sweat, feces, sputum, and other bodily fluids (Ramachandran and Swaminathan, 2015). These adverse effects are reversible after clofazimine cessation, but may take months to years to fully resolve (Moore, 1983; Ramachandran and Swaminathan, 2015). Ichythosis is reported to occur in 8–66% of patients treated with clofazimine (Ramachandran and Swaminathan, 2015; Tang *et al.*, 2015), and other rashes occur in 1–5% of patients (Ramachandran and Swaminathan, 2015). Despite their frequency, most clinical studies report that very few patients discontinue clofazimine as a result of dermatological side effects (Hwang *et al.*, 2014; Karat *et al.*, 1970; Karat *et al.*, 1971; Padayatchi *et al.*, 2014). However, the drug prescribing information published by the manufacturer cited a report of a suicide in association with depression secondary to skin discoloration (Novartis Pharma, 2005). Lymphedema and exfoliative dermatitis have rarely been reported with clofazimine use (Oommen, 1990; Pavithran, 1985; Tyagi and Oommen, 1993).

6b. Gastrointestinal adverse effects

Abdominal pain, nausea, vomiting, and diarrhea are reported in up to 40–50% of patients taking clofazimine (Moore,