2 production from macrophages (Iwanaga et al. 2015). Similarly, erythromycin (and roxithromycin) stimulates neutrophil migration *in vitro* (Anderson 1989).

Study of the immunomudulatory activities of macrolides has led to the exploration of non-antibacterial erythromycin derivatives. Less potent macrolides (GS-459755 [2′-desoxy-9-(*S*)-erythromycylamine] and GSA-560660 [azithromycin-based 2′-desoxy molecules]) are under development to reduce inflammation via inhibition of the NLRP3 inflammasome in chronic lung diseases while at the same time not affecting increases in rates of bacterial resistance (Hodge et al. 2017). Other non-antibacterial macrolides are well known for their use in modification of the immune system. Tacrolimus is a macrolide immunosuppressant/immunomodulator that is a calcineurin inhibitor and therefore suppresses T-cell activity (Kitahara and Kawai 2007).

5.4 Clinical Use of Macrolides

In the United States, the Food Drug Administration has approved five macrolide antibiotics: erythromycin, clarithromycin, azithromycin, dirithromycin, and telithromycin. Several non-antibiotic macrolides have also been approved for clinical use and include the immunosuppressives rapamycin and tacrolimus, as well as the antifungals amphotericin B and nystatin A1. Orphan drug status has been given to cethromycin for some prophylactic treatments. Macrolides have been classified as critically important to human medicine by the Federal Drug Administration (Powers 1998). Globally, a broader variety of macrolides have been approved for use and include the following: spiramycin, rokitamycin, midecamycin, kitasamycin/leucomycin, josamycin, trichomycin (antifungal and antiprotozoal), and pimaricin/natamycin (antifungal).

Macrolides have varied bioavailability. Erythromycin is highly acid labile and has the lowest bioavailability, which varies greatly with the formulation (Ginsburg 1986). As previously noted, due to its similarity to motilin, erythromycin is associated with gastrointestinal motor-stimulating activity and accompanying side effects (Omura et al. 1985). Other macrolides are more acid stable and as a result have both increased bioavailability and reduced gastrointestinal side effects – in the case of clarithromycin and telithromycin, 52–55 and 57% bioavailability, respectively (Chu et al. 1992; Douthwaite et al. 2000). Upon oral administration, clarithromycin is converted into a 14-hydroxy metabolite, which accounts for the majority of clarithromycin's antimicrobial activity (Chu et al. 1992). Clarithromycin and other 14-membered macrolides are oxidized by hepatic enzymes in the cytochrome P450 system by the CYP3A subclass of enzymes (Rodrigues et al. 1997). They inhibit CYP3A; however, azithromycin does not, nor do the ketolides (Chavan et al. 2016).