PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERIZATION OF THE PLEUROMUTILIN ANTIBIOTIC RETAPAMULIN

By

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Retapamulin, an antibiotic from the pleuromutilin class, is approved to treat impetigo, a skin disease frequently caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. It inhibits the bacterial protein synthesis by binding to the 50s subunit of the bacterial ribosome and has a unique mechanism of action. Currently, retapamulin is marketed as topical ointment for use in adults and pediatric patients.

Pharmacokinetic data on retapamulin is limited due to low systemic exposure after topical application. No pharmacokinetic parameters have been established for retapamulin and concentrations at the site of action have yet to be evaluated. To characterize the pharmacokinetics, dermal concentrations of retapamulin where quantified by microdialysis and compared to plasma concentrations.

The pharmacodynamics of retapamulin were assessed using *in vitro* time-kill curve experiments against methicillin-susceptible *Staphylococcus aureus* (MSSA). Although retapamulin is indicated to treat MSSA infections only, the activity against methicillin-resistant *Staphylococcus aureus* (MRSA) was also investigated and compared to that of MSSA.
Pharmacokinetics were evaluated with non-compartmental and compartmental analysis and integrated with a semi-mechanistic pharmacodynamic model to quantify and predict retapamulin’s concentration-effect relationship under different dosing regimens.