

Development of an Intravenous Formulation of Solithromycin (CEM-101), a Novel, Potent Fluoroketolide

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Background:

Solithromycin (CEM-101) is a potent new fluoroketolide under development for the treatment of bacterial respiratory tract and other infections. In order to treat moderate to moderately severe to severe community acquired bacterial pneumonia (CABP), an intravenous formulation of Solithromycin is desirable.

Methods:

A soluble, stable formulation of Solithromycin was developed and tested in 28-day toxicology studies in dogs and monkeys.

CEM-101 was infused once daily at doses of 0, 5, 10 and 15 mg/kg in dogs and at doses of 0, 5, 12.5 and 25 mg/kg in monkeys. Blood was drawn pre-dose and at 0, 0.5, 1, 4, 8, 12 (monkey) and 24 hours following cessation of dosing on days 1 and 28 for pharmacokinetic measurements. Clinical pathology and histopathology evaluations were performed.

Results:

Unlike other macrolides, it was noted that there was no apparent pain and no significant irritation at the injection sites with Solithromycin. Excellent blood levels were achieved in both species. In the dog, the C_{max} of the 15 mg/kg dose group on days 1 and 28 were 3.9 mg/L and 3.0 mg/L, respectively. There were no toxicologically significant serum chemistry, hematology or coagulation changes. Injection site had minor microscopic changes, mostly procedure related. Monkey plasma C_{max} at 25 mg/kg were 5.4 mg/L on Day 1 and 5.9 mg/L on Day 28. There were no toxicologically significant serum chemistry, hematology or coagulation changes. Injection sites had minor microscopic changes, mostly procedure related. Overall, there was little variability in blood levels and no cardiac or other pharmacological abnormalities were noted in the dog or monkey.

Conclusions:

The toxicology assessment for the intravenous product of Solithromycin has been successfully completed. Solithromycin was well tolerated with only minimal and reversible findings. Solithromycin is the first macrolide/ketolide since azithromycin to have the potential for an intravenous formulation making it feasible to conduct trials with a macrolide in moderately severe to severe CABP.