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

P. Fernandes, T. Degenhardt, D. Pereira
Cempra Pharmaceuticals, Inc., Chapel Hill, North Carolina

Abstract

Background: Solithromycin (CEM-101) is a novel potent 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 scalable, stable formulation of Solithromycin was developed and tested in 28-day toxicity studies in dogs and monkeys. CEM-101 was infused once daily at doses of 5, 5, 10 and 15 mg/kg in dogs and at doses of 5, 12.5 and 25 mg/kg in monkeys. Blood was drawn pre-dose and at 0, 0.5, 1, 4, 8, and 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 Cmax of the 15 mg/kg dose group on days 1 and 28 were 3.9 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 Cmax at 25 mg/kg was 5.4 mg/L, on Day 1 and 5.9 mg/L, on Day 26. There were no toxicologically significant serum chemistry, hematology or coagulation changes. Injection sites had minor microscopic changes, mostly procedure related. Overall, there were little variability in blood levels and no cardiac or other pharmacological abnormalities were noted in the dog or monkey.

Conclusion: The toxicity 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 solithromycin to have the potential for an intravenous formulation making it feasible to conduct trials with a macrolide in moderately to severe CABP.

Materials and Methods

Introduction

An intravenous (IV) formulation of solithromycin is being developed in an effort to provide treatment for older patients with more severe CABP. The IV formulation followed by the oral formulation could slow step-down therapy for appropriate patients, and thereby provide a benefit over an oral formulation alone.

Many experiments have been conducted toward the development of a suitable IV formulation, and were based upon past experience and available information on IV formulations of macrolides.

Results

28-day Repeat-dose Toxicity in Dogs

Solithromycin at doses up to 15 mg/kg by intravenous infusion for 28 consecutive days was well tolerated. Administration of 15 mg/kg resulted in the phenotypic appearance of one macrolide-resistant strain from the study population. Blood levels were similar in dogs and monkeys. The plasma exposure of solithromycin was similar in both species. In addition, there were no toxicologically significant changes in body weight, food consumption, or clinical pathology. There were no toxicologically significant changes in cardiac rhythm or heart rate. The drug was eliminated in urine and feces with minimal enterohepatic recycling.

Discussion

Conclusion: Solithromycin is being developed as a novel potent fluoroketolide 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. Solithromycin has been developed as a scalable, stable formulation and tested in 28-day toxicity studies in dogs and monkeys. Solithromycin is well tolerated in dogs and monkeys after repeated daily IV dosing for 28 days on IV formulations in dogs and monkeys. Solithromycin was administered to cynomolgus monkeys at doses of 5, 12.5 and 25 mg/kg via intravenous infusion into the ophthalmic or brachial veins for 28 days.

References