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CEM-102 (Sodium Fusidate) Dosage Regimen Decision Support Using Population Pharmacokinetic (PPK) and Mechanism-Based Pharmacokinetic-Pharmacodynamic (PK-PD) Models

Biography:

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Dr. Forrest completed his Doctorate in Pharmacy in 1979 at the University of Southern California. He was a Post Graduate Research Scholar, in Clinical Pharmacology, in Roger Jeffille's Laboratory of Applied Pharmacokinetics at the USC School of Medicine. Dr. Forrest then became a faculty member, at the USC Schools of Pharmacy and of Medicine. He next was at the University of Maryland in Baltimore, Schools of Pharmacy and of Medicine as an Assistant Professor (Clinical Pharmacy, Infectious Diseases and Oncology) from 1982 to 1989 and has been at the State University of New York at Buffalo, Schools of Pharmacy, Medicine and Public Health since 1989. His current SUNY appointments are as a Research Professor in the Departments of Pharmacy Practice and of Pharmaceutics, in the School of Pharmacy and Biostatistics, in the School of Public Health. Dr. Forrest is also a Senior Scientist in Pharmacometrics, in the Institute of Clinical Pharmacodynamics within the Ordway research Institute, since 2005.

Dr. Forrest's main expertise is in pharmacometrics (advanced applications of pharmacokinetic-pharmacodynamic system analysis). His research spans all drug classes but has emphasized infectious diseases and oncology. His special research interests are in clinical research applications of adaptive feedback control in the optimization of drug therapy, individual and population pharmacokinetic-pharmacodynamic modeling, translational pharmacokinetic-pharmacodynamic research in drug development and development and validation of optimal pharmacokinetic-pharmacodynamic study designs.

Dr. Forrest is the author or co-author of five book chapters and 190 publications in peer-reviewed journals. He has made more than 70 invited presentations and he is the author or co-author of over 400 peer-reviewed abstracts for national and international symposia. He has presented numerous other invited presentations, including at the Food and Drug Administration, the National Institutes of Health, universities, institutions, medical centers, and pharmaceutical companies.

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Abstract:

Background: CEM-102, an oral antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), is in

development for the treatment of complicated skin and skin structure infections. Using previously-developed PPK and mechanism-based PK-PD models, Monte Carlo simulation (MCS) was conducted to evaluate CEM-102 dosing regimens, with and without front-loading (FL), for future clinical trials.

Methods: MCS was performed using S-ADAPT and parameter estimates from a PPK and a mechanism-based PK-PD model. The two-compartment PPK model with auto-inhibition of clearance was based on data from 69 subjects who received CEM-102 500 to 2200 mg orally, as single and/or multiple doses. The mechanism-based PK-PD model was based on data from an *in vitro* PK-PD model that evaluated 7 CEM-102 regimens against MRSA USA300 (MIC 0.25 µg/mL) over 48 h. Antibacterial effects of CEM-102 were assessed by evaluating the log₁₀ ratio (LR) of the area under the colony forming unit curve (AUC_{CFU}) for each regimen relative to the AUC_{CFU} for the growth control (GC) at 24 and 48 h, the CFU nadir at 24 and 48 h, time to nadir (T_n) and time to return to baseline or net bacterial stasis (T_s). The following 7 CEM-102 regimens were evaluated: 500 mg Q12h; 600 mg Q12h; 500 mg Q8h, 600 mg Q12h starting on Day 2 with FL of either 900, 1200, or 1500 mg Q12h on Day 1; and 900 mg Q12h starting on Day 2 with FL of 1500 mg Q12h on Day 1.

Results: Median LRs of the AUC_{CFU} relative to that of the GC at 24 h were similar across all 7 regimens (-2.29 to -2.32). At 48 h, non-FL regimens had median LRs of -0.89 to -1.31 (88 to 95% reduction in AUC_{CFU} compared to GC). The 3 regimens with FL ≥ 2400 mg followed by 900 or 600 mg Q12h had LRs at 48 h of -2.07 to -2.36 (99.1% to 99.6% less AUC_{CFU}). Median T_n and T_s ranged from 17.2 to 19.0 and 25.7 to 29.9 h for non-FL and 24.4 to 27.7 and 39.1 to 45.1 h, for FL ≥ 2400 mg regimens, respectively.

Conclusion: CEM-102 antibacterial effects were substantially better after FL. CEM-102 dosage regimens with FL of ≥ 2400 mg on Day 1 followed by 600 mg Q12h starting on Day 2 should be appropriate to treat CEM-102-susceptible strains of *S. aureus*.

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