Population pharmacokinetics of lenalidomide in patients with haematological cancer

Jim H. Hughes1,2, Stephanie E. Reuter2, Richard N. Upton1,2, Mitch A. Phelps3, David J.R. Foster1,2

1 Australian Centre for Pharmacometrics, School of Pharmacy and Medical Sciences, University of South Australia 2 School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia 3 Comprehensive Cancer Center, The Ohio State University

Objectives: Lenalidomide is an immunomodulatory imide drug used in the treatment of multiple myeloma (MM), but is not used in chronic lymphocytic leukaemia (CLL) due to presumed dose-related toxicity. This study aimed to develop a population pharmacokinetic model for lenalidomide in multiple cancers, including CLL, to identify any disease-related differences in disposition.

Methods: Lenalidomide concentrations from four clinical trials were collated (1999 samples, 125 subjects), covering four cancers (MM, CLL, acute myeloid leukaemia and acute lymphoblastic leukaemia) and a large dose range (2.5 – 75mg). A population pharmacokinetic model was developed with NONMEM. Creatinine clearance (CrCL), cancer type, body weight and other patient demographics were tested as covariates.

Results: The data was best fit by one-compartment kinetic model with a seven transit absorption model. A proportional error model was found to best describe the residual error. Parameters were scaled for fat-free mass according to allometric theory. The population parameter estimates for apparent clearance, apparent volume of distribution and transit rate constant were 12 L/h, 68.8 L, and 13.5 h⁻¹ respectively. The transit rate constant had significant between subject variability to account for variability in absorption. Creatinine clearance was found as a continuous covariate, such that patients with impaired renal function (CrCL 30 mL/min) exhibit a 22% reduction in lenalidomide clearance compared to patients with CrCL of 90mL/min. Cancer type had no discernible effect on lenalidomide disposition.

Conclusions: This is the first report of a lenalidomide population pharmacokinetic model in multiple malignancies. This model is intended to inform future clinical studies discerning the pharmacokinetics of lenalidomide and its use in CLL.