Prophylaxis of Gout Flares in Patients with Renal Impairment: Dosing Adjustments with Colchicine Oral Solution Informed by a Pharmacokinetic Model

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INTRODUCTION

Colchicine is a first-line anti-inflammatory prophylaxis agent recommended for gout patients when urate lowering therapy (ULT) is initiated[1]. The anti-inflammatory effects of colchicine are mostly determined by intracellular accumulation and its serum concentrations relate poorly to efficacy, but modeling serum levels is a useful guide to determine drug safety. The effective steady-state range of colchicine plasma concentrations is 0.5 – 3.0 ng/mL[2] with plasma levels above the 3.0 ng/ml limit resulting in toxicity and levels below 0.5 ng/ml likely resulting in subtherapeutic dosing.

Per ACR Guidelines, colchicine dose reduction is recommended in patients with moderate and severe renal impairment. In an open-label pharmacokinetic study, the clearance of colchicine in the moderate renal impairment group was observed to be approximately half of the value of normal subjects[3]. This information on decrease in colchicine clearance was applied to the pharmacokinetic model fit parameters of colchicine oral solution (Gloperba®) in healthy subjects and simulated for different clearance rates (i.e.; 30%, 50% and 70%). Recommended colchicine starting doses that will maintain the steady state colchicine levels in the therapeutic range were identified in patients with moderate and severe renal impairment.

METHODS

Gloperba Bioavailability Study:

A randomized, open-label, single-dose bioavailability, and food effect study in 34 healthy subjects of colchicine oral solution 0.6 mg (5 mL) vs. probenecid/colchicine tablets (500 mg/0.5 mg) supported the Food and Drug Administration approval of colchicine oral solution (Gloperba) for the prophylaxis of gout flares.

Summary of Relative Bioavailability Analysis for Test vs. Reference of Colchicine - PK Population

PK Parameter	Least Squares Geometric Means				Percent Ratio of Geometric Means (%)	Percent Ratio of Geometric Means 90% CI (%)	Intra-Subject CV%
	n	A	n	C	A/C	A/C	
C_{max}/Dose (ng/mL/mg)	34	3.356	34	3.408	98.45	(88.47 - 109.6)	26.86
AUC_{0-t}/Dose (ng*hr/mL/mg)	34	30.09	34	29.72	101.2	(94.05 - 109.0)	18.33
AUC_{0-inf}/Dose (ng*hr/mL/mg)	34	32.32	34	32.16	100.5	(93.86 - 107.6)	16.95

A = Colchicine Oral Solution 0.6 mg (0.12 mg/mL, 5mL), Fasted
C = Probenecid and Colchicine Tablets (500 mg/0.5mg), Fasted

- The comparisons of colchicine exposure (dose normalized C_{max}, AUC_{0-t} and AUC_{0-inf}) between the test (oral solution) and reference formulation (tablet) satisfied bioequivalence criteria.
- Minimum food effect was observed.

Data Analysis:

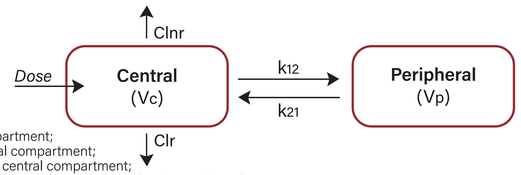
Mean plasma concentration time data from the above study were used to build a pharmacokinetic model using Phoenix 64® WinNonlin® software version 8.1 (Certara, USA).

The pharmacokinetic model that best fitted the mean plasma concentration time profile for colchicine oral solution was a two-compartment model with a lag time.

Model appropriateness was based on a few model selection criteria including the measure of goodness of fit as determined by the Akaike's information criterion (AIC) and Schwartz Bayesian criterion (SBC).

Structural Pharmacokinetic Model:

A schematic representation of the pharmacokinetic model used for the simulations.



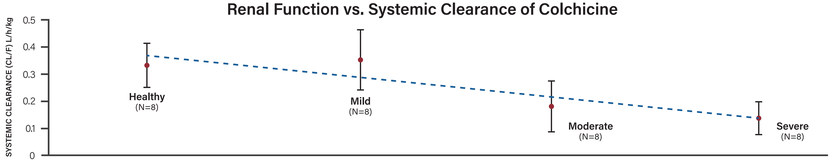
- Vc, volume of distribution of the central compartment;
- Clr, first-order renal clearance from the central compartment;
- Clnr, first-order non-renal clearance from the central compartment;
- k12, first-order intercompartmental transfer constant from the central to the peripheral compartment;
- k21, first-order inter-compartmental transfer constant from the peripheral to the central compartment;

Results of Renal Impairment Study with Colchicine:

Change (x-fold) in Pharmacokinetic Parameters Relative to Normal[3] (Wason et al 2014)

PK Parameter	Healthy Subjects with Normal Renal Function	Mild RI	Moderate RI	Severe RI
C_{max}(ng/mL)	1.0	1.12x	1.52x	1.04x
$t_{1/2}$(h)	1.0	1.01x	1.30x	1.62x
$AUC_{0-\infty}$(ng·h/mL)	1.0	1.10x	1.98x	1.94x
CL/F (L/h/kg)	1.0	1.06x	0.53x	0.41x

Renal Function vs. Systemic Clearance of Colchicine



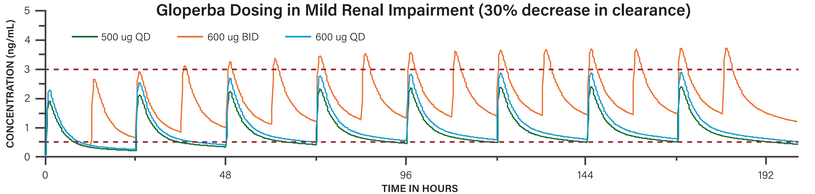
Simulation Assumptions for Colchicine Oral Solution Dosing:

- Consider the best fit pharmacokinetic model parameters derived from healthy subjects.
- Use the findings from Wason et al. (2014).
- Adjusted the disposition parameters for different degrees of colchicine clearance (i.e.; 30%, 50%, and 70%).

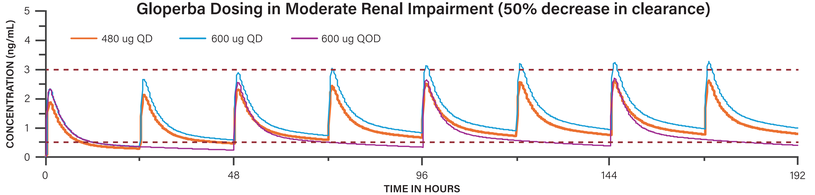
Parameters	Mild (30% impaired)	Moderate (50% impaired)	Severe (70% impaired)
V (L)	204	204	204
K10 (1/h)	0.108	0.0775	0.046
K12 (1/h)	0.175	0.175	0.175
K21 (1/h)	0.067	0.067	0.067
TL (hr)	0.189	0.189	0.189

RESULTS

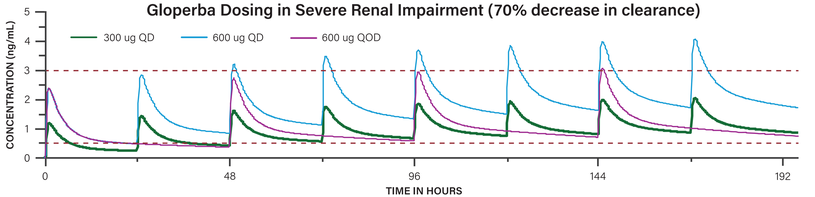
Gloperba Dosing in Mild Renal Impairment (30% decrease in clearance)



Gloperba Dosing in Moderate Renal Impairment (50% decrease in clearance)



Gloperba Dosing in Severe Renal Impairment (70% decrease in clearance)



Summary:

Currently available formulations of colchicine do not deliver the precise dosing needed in gout patients with CKD.

Visual inspections of the simulated profiles above for different levels of renal impairment reveals that:

- For 30% decrease in clearance (mild renal impairment) - Dose of 0.6 mg (5 mL) QD maintains drug levels in therapeutic window at steady state.
- For 50% decrease in clearance (moderate renal impairment) - Dose of 0.48 mg (4 mL) QD maintains drug levels in therapeutic window at steady state.
- For 70% decrease in clearance (severe renal impairment) - Dose of 0.3 mg (2.5 mL) QD maintains the drug levels in therapeutic window at steady state.

Alternate dosing regimens (i.e.; BID or QOD) result in drug concentrations outside the therapeutic window for a substantial period of the dosing interval.

Gloperba is the first and only oral solution of colchicine for prophylaxis of gout designed to deliver precise dosing in patients with moderate or severe CKD.

1. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken). 2020;72(6):744–760. 2. Niel E, Scherrmann JM. Colchicine today. Joint Bone Spine 2006;73:672-678. 3. Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. Clin Drug Investig. 2014;34(12):845-55. 6. Scilex Holding. Gloperba prescribing information 2024.