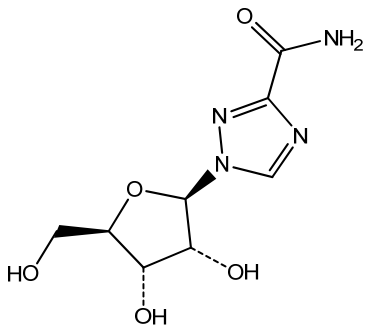
Ribavirin PK Fact Sheet

Details

Generic Name	Ribavirin/Tribavirin
Trade Name	Copegus®, Rebetol®
Class	Broad spectrum antiviral – nucleoside analogue of guanine
Molecular Weight	244.2
Structure	

Summary of Key Pharmacokinetic Parameters

High inter- and intra-subject pharmacokinetic variability is observed following single oral dose (intra-subject variability ~30% for AUC and Cmax). Accumulation in plasma is extensive with multiple dosing.

Linearity/non-linearity	Linear relationship between dose and AUC following single doses of 200-1200 mg. Curvilinear relationship between dose and Cmax, tending to asymptote above single doses of 400 to 600 mg.
Steady state	Upon multiple dosing, ribavirin accumulates extensively in plasma with a 6-fold ratio of multiple-dose to single-dose AUC12h. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately four weeks. Upon discontinuation of dosing the half-life was ~298 hours, which probably reflects slow elimination from non-plasma compartments.
Plasma half life	140-160 h for single doses, Copegus® tablets 79 h, single dose, Rebetol® capsules ~300 h for multiple doses
Cmax	872 ng/ml (600 mg oral solution, single dose, Rebetol® solution) 782 ng/ml (600 mg, single dose, Rebetol® capsules) 3680 ng/ml (600 mg twice daily multiple dose, Rebetol® capsules) 2748 ± 818 ng/ml (1200 mg/day, 12 weeks dosing, Copegus® tablets)
Cmin	1662±545 ng/ml (800 mg/day, 12 weeks dosing, Copegus® tablets) 2112±810 ng/ml (1200 mg/day, 12 weeks dosing, Copegus® tablets)
AUC	14098 ng.h/ml (600 mg oral solution, single dose, Rebetol® solution) 13400 ng.h/ml (600 mg, single dose, Rebetol® capsules) 228000 ng.h/ml (600 mg twice daily multiple dose, Rebetol® capsules) 25361 ± 7110 ng.h/ml (1200 mg/day, 12 weeks dosing, Copegus® tablets)
Bioavailability	~45-65%
Absorption	Bioavailability of a single oral 600 mg dose is increased by coadministration of a high fat meal, as compared to fasting. The manufacturers of Copegus® recommend ribavirin is taken with food.
Protein Binding	Does not bind to plasma proteins
Volume of Distribution	~4500-5000 L
CSF:Plasma ratio	Data not available
Semen:Plasma ratio	Data not available

Renal Clearance	Ribavirin and its metabolites are excreted renally (61%, of which 17% is parent drug). The manufacturers of Copegus® report that clearance increases as a function of body weight and is predicted to vary from 17.7 to 24.8 L/h over a weight range of 44 to 155 kg. The manufacturers of Rebetol® advise that this effect is not clinically significant.
Renal Impairment	Apparent clearance of ribavirin is reduced in renal dysfunction and the manufacturers recommend that renal function is evaluated prior to initiation. There are insufficient data for creatinine clearance <50 ml/min to support recommendations for dose adjustments. The manufacturers of Copegus® advise that ribavirin should be used in these patients only when considered essential, and that it be used with extreme caution and intensive monitoring of haemoglobin concentrations. The manufacturers of Rebetol® recommend that patients with CrCl <50 ml/min should not be treated. Ribavirin concentrations are essentially unchanged by haemodialysis.
Hepatic Impairment	Hepatic function does not affect the pharmacokinetics of ribavirin, therefore, no dose adjustment is required in hepatic impairment. However, use is contraindicated in severe hepatic dysfunction or decompensated cirrhosis of the liver.

Metabolism and Distribution

Metabolised by	Two possible pathways: reversible phosphorylation or degradation involving deribosylation and amide hydrolysis. No CYP450 mediated metabolism.
Inducer of	Does not induce liver enzymes.
Inhibitor of	Does not inhibit CYP450 enzymes.
Transported by	Nucleoside transporters: hCNT2, hCNT3, hENT1, hENT2[1].

References

Unless otherwise stated (see below), information is from:
Copegus® Tablets Summary of Product Characteristics, Roche Ltd.
Rebetol® Capsules Summary of Product Characteristics, Schering-Plough Ltd.
Copegus® Tablets US Prescribing Information, Genentech Inc.
Rebetol® US Prescribing Information, Schering-Plough Ltd.

1. Yamamoto T, Kuniki K, Takekuma Y et al. Ribavirin uptake by cultured human choriocarcinoma (BeWo) cells and Xenopus laevis oocytes expressing recombinant plasma membrane human nucleoside transporters. *Eur J Pharmacol* 2007; **557:** 1-8.