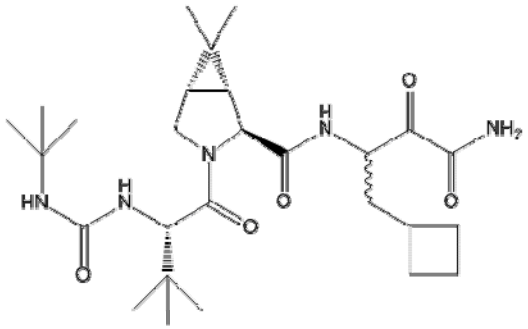
Boceprevir PK Fact Sheet

Details

Generic Name	Boceprevir
Trade Name	Victrelis®
Class	HCV NS3/4A protease inhibitor
Molecular Weight	519.7
Structure	

Summary of Key Pharmacokinetic Parameters

Boceprevir capsules contain a 1:1 mixture of two diastereomers, SCH534128 and SCH534129. In plasma the diastereomer ratio changes to 2:1, favouring the active diastereomer, SCH534128. Plasma concentrations of boceprevir described below consist of both diastereomers SCH534128 and SCH534129, unless otherwise specified.

Linearity/non-linearity	Steady state AUC, Cmax, and Cmin increased in a less-than-dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1200 mg, suggesting diminished absorption at higher doses.
Steady state	Achieved after approximately 1 day of three times daily dosing.
Plasma half life	~3.4 h
Cmax	1723 ng/ml (800 mg three times daily)
Cmin	88 ng/ml (800 mg three times daily); although population PK modelling in two pivotal phase III trials gave a median Cmin of 212 ng/ml.
AUC	5408 ng.h/ml (800 mg three times daily)
Bioavailability	Formal bioavailability not determined.
Absorption	Boceprevir should be administered with food. Food enhanced the exposure of boceprevir by up to 65% at the 800 mg three times daily dose, relative to the fasting state. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, boceprevir may be taken without regard to either meal type or timing of the meal.
Protein Binding	~75%
Volume of Distribution	~ 772 L
CSF:Plasma ratio	Not studied
Semen:Plasma ratio	Not studied
Renal Clearance	~3% excreted as unchanged boceprevir in the urine.
Renal Impairment	No dosage adjustment of boceprevir is required in patients with any degree of renal impairment. The mean AUC of a single 800 mg boceprevir was 10% lower in subjects with end stage renal disease requiring haemodialysis relative to subjects with normal renal function. Haemodialysis removed less than 1% of the boceprevir dose.

Hepatic Impairment	No dosage adjustment of boceprevir is recommended for patients with mild, moderate or severe hepatic impairment. The pharmacokinetics of boceprevir was studied in adult non-HCV infected subjects with normal, mild (Child-Pugh score 5-6), moderate (Child-Pugh score 7-9), and severe (Child-Pugh score 10-12) hepatic impairment following a single 400 mg dose of boceprevir. The mean AUC of the active diastereomer of boceprevir (SCH534128) was 32% and 45% higher in subjects with moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. Mean Cmax values for SCH534128 were 28% and 62% higher in moderate and severe hepatic impairment, respectively. Subjects with mild hepatic impairment had similar SCH534128 exposure as subjects with normal hepatic function. A similar magnitude of effect is anticipated for boceprevir. The safety and efficacy of boceprevir have not been studied in patients with decompensated cirrhosis.

Metabolism and Distribution

Metabolised by	Primarily metabolised by aldo-ketoreductase to inactive ketone-reduced metabolites. Partly metabolised by CYP3A4/5.
Inducer of	Does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 in vitro.
Inhibitor of	Strong inhibitor of CYP3A4/5. Does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 in vitro. Potential inhibitor of P-gp based on in vitro studies.
Transported by	P-gp

References

Unless otherwise stated (see below), information is from:
Victrelis® Summary of Product Characteristics, Merck Sharp & Dohme Ltd.
Victrelis® US Prescribing Information, Merck & Co Inc..