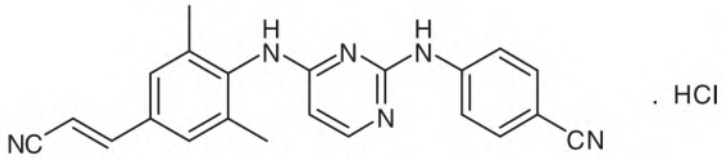
Rilpivirine (oral) PK Fact Sheet

Details

Generic Name	Rilpivirine
Trade Name	Edurant®
Class	Non-Nucleoside Reverse Transcriptase Inhibitor
Molecular Weight	402.88 (as rilpivirine hydrochloride)
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	Over the dose range 25-150 mg once daily, plasma concentrations obtained following administration of a tablet formulation to healthy volunteers increased in a dose-proportional manner [1].
Steady state	Steady state is anticipated to be achieved in ~10-15 days [2].
Plasma half life	~45-50 h
Cmax	204 ± 76 ng/ml (n=12, healthy volunteers) [1] (Population PK estimate not available)
Cmin	67 ± 30 ng/ml (n=12, healthy volunteers) [1] 73 (2-288) ng/ml, predicted median (range) from population PK modelling (n=679, HIV+)
AUC	2589 ± 869 ng.h/ml (n=12, healthy volunteers) [1] 2096 (198-7307) ng.h/ml, predicted median (range) from population PK modelling (n=679, HIV+)
Bioavailability	Absolute bioavailability not determined due to lack of an IV formulation [2]
Absorption	Rilpivirine must be taken with a meal. The exposure to rilpivirine was approximately 40% lower when rilpivirine was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high fat high-caloric meal (928 kcal). When rilpivirine was taken with only a protein rich nutritional drink, exposures were 50% lower than when taken with a meal. Coadministration of rilpivirine with products that increase gastric pH may decrease rilpivirine plasma concentrations.
Protein Binding	99.7%
Volume of Distribution	~152 L [2]
CSF:Plasma ratio	Not evaluated in humans
Semen:Plasma ratio	Not evaluated in humans
Renal Clearance	6.1%; <1% as unchanged drug

Dosing in Renal and Hepatic Impairment

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution and with increased monitoring for adverse effects, as rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic Impairment

In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment, but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) and is not recommended in these patients.

Metabolism and Distribution

Metabolised by

Primarily CYP 3A. Potential contribution from CYP2C19 [2].

Inducer of

At the recommended dose of 25 mg once daily, rilpivirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

Inhibitor of

Rilpivirine inhibits P-gp in vitro with an IC50 of 9.2 µM. In a clinical study, rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure of other medicines transported by P-gp that are more sensitive to intestinal P-gp inhibition, e.g. dabigatran etexilate.

Rilpivirine is an in vitro inhibitor of the transporter MATE-2K with an IC50 of <2.7 nM. The clinical implications of this finding are currently unknown.

Transported by

Not significantly transported by P-gp [2].

References

Unless otherwise stated (see below), information is from:
Edurant® Summary of Product Characteristics, Janssen-Cilag Ltd.
Edurant® US Prescribing Information, Janssen Pharmaceuticals Inc.

1. Hoetelmans R, Van Heeswijk R, Kestens D, *et al.* Effect of food and multiple-dose pharmacokinetics of TMC278 as an oral tablet formulation. 3rd IAS Conference on HIV Pathogenesis and Treatment, Brazil, July 2005, abstract TuPe3.1B10.
2. FDA, Rilpivirine Clinical Pharmacology and Biopharmaceutics Review (NDA 202-022) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202022Orig1s000TOC.cfm