

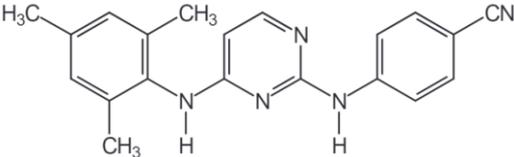
Dapivirine (VR) PK Fact Sheet

Produced July 2021

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Details

Generic Name	Dapivirine
Trade Name	N/A
Class	Non-Nucleoside Reverse Transcriptase Inhibitor
Molecular Weight	329.41
Structure	

Summary of Key Pharmacokinetic Parameters

The dapivirine vaginal ring (VR) contains 25 mg of dapivirine and delivers approximately 4 mg of dapivirine topically to the lower female reproductive tract over a period of 28 days.

<i>Linearity/non-linearity</i>	Dapivirine concentrations in fluids and tissues were not dose proportional when comparing extended duration rings (100 mg and 200 mg for 13 weeks) and the 25 mg monthly ring. ^[1]
<i>Steady state</i>	Dapivirine is released from the ring in a sustained manner, distributed into vaginal fluid, and absorbed into surrounding tissues and plasma. Measurable dapivirine concentrations were detected in vaginal fluid and plasma within 1-4 h after ring insertion. Dapivirine concentrations in vaginal fluid exceeding the in vitro HIV-1 IC99 by 1000-fold are achieved within 24 h of ring insertion. At 4-24 h after ring insertion, vaginal fluid concentrations (at all 3 sampling locations: cervix, ring area and introitus) are similar to those on day 28 after continuous ring use. Dapivirine plasma concentrations at 24 h after ring insertion are also similar to those at 28 days after continuous ring use. Systemic concentrations of dapivirine observed in plasma with the use of the dapivirine VR were low (< 2 ng/mL).
<i>Half life</i>	Plasma: 81.5 h Vaginal fluid (cervix): 13.1 h
<i>Cmax</i>	Plasma: 462 pg/ml Vaginal fluid (cervix): 76.9 µg/g
<i>Ctau (day 28)</i>	Plasma: 291.0 pg/ml Vaginal fluid (cervix): 22.78 µg/g
<i>AUC (0-28 days)</i>	Plasma: 229408 pg.h/ml Vaginal fluid (cervix): 24222 µg.h/g
<i>Bioavailability</i>	Not yet determined.
<i>Absorption</i>	Cervical tissue biopsies were evaluated in two clinical trials. Interindividual dapivirine concentrations in tissue at day 28 were highly variable (46-12900 ng/ml). However, the lowest measured dapivirine concentration was still 10 times the in vitro IC99 in cervical tissue.
<i>Protein Binding</i>	Plasma:>99.6% Vaginal fluid (cervix): 15%
<i>Volume of Distribution</i>	Vaginal fluid (cervix): 11.1 g ^[2]
<i>CSF:Plasma ratio</i>	Not evaluated
<i>Semen:Plasma ratio</i>	N/A
<i>Renal Clearance</i>	Orally administered dapivirine was shown to undergo negligible renal clearance.

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Dosing in Renal and Hepatic Impairment

<i>Renal Impairment</i>	No clinical trials in women with renal impairment have been performed. Based on low plasma concentrations and negligible renal clearance of dapivirine, renal impairment is not expected to affect dapivirine exposure or the safety profile.
<i>Hepatic Impairment</i>	No clinical trials in women with hepatic impairment have been performed. In view of the low systemic exposure of dapivirine, hepatic impairment is not expected to affect dapivirine exposure or the safety profile.

Metabolism and Distribution

<i>Metabolised by</i>	CYP450 (primarily CYP3A4/5, with contributions from CYP2B6 and CYP2C19 [2]), UGT1A, UGT2B. In vaginal tissue, CYP450, but not UGT enzyme activity was detected.
<i>Inducer of</i>	Not an inducer of CYP1A2, CYP3A4 or CYP3A5 in human hepatocytes at concentrations up to 100 ng/ml.
<i>Inhibitor of</i>	Due to the low plasma concentrations of dapivirine, no effect of dapivirine on the exposure of systemically co-administered drugs, that are either a substrate for CYP enzymes or transporters, is expected. [2]
<i>Transported by</i>	Not transported by P-gp.

References

Unless otherwise stated (see below), information is from:

Dapivirine Vaginal Ring® [Summary of Product Characteristics](#), International Partnership for Microbicides.

1. Phase 1 pharmacokinetics and safety study of extended duration dapivirine vaginal rings in the United States. Liu AY, Dominguez Islas C, Gundacker H, et al. *J Int AIDS Soc*, 2021, 24:e25747.
2. Dapivirine vaginal ring 25 mg: European Medicines Agency Public Assessment Report. https://www.ema.europa.eu/documents/outside-eu-assessment-report/dapivirine-vaginal-ring-25-mg-public-assessment-report_en.pdf