Selected Properties of Ritonavir

Other names	Norvir®, ABT-538
Manufacturer	Abbott Laboratories, Ltd.
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	IC90: 0.11 uM (in vitro) WT IC50: 0.007-0.0436 uM (Phenosense)
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: V82A/F/T/S, I84V Minor: L10F/I/R/V, K20R/M, V32I, L33F, M36I, M46I/L, I50V, I54V/L, A71V/T, V77I, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): V82A/T/F/S : 1.3- to 4-fold ↑ 84V: 4.3-fold ↑ 84V, 90M: 17-fold ↑ 54V, 82A, 90M: 84-fold ↑ (high resistance) 54V, 82A: 22-fold ↑ 46I/V, 54V, 82A: 30- to 40-fold ↑ (high resistance)
Cross-Resistance	Cross- resistance with other PI's seen.
Oral Bioavailability	Absolute bioavailability not determined.
Effect of Food	Capsules: • food ↑ AUC by 13% Tablets (100 mg single dose): • with high fat meal (907 kcal; 52% fat, 15% protein, 33% carbohydrates), 23% ↓ in mean AUC, 23% ↓ in mean C_{max} relative to fasting conditions • with moderate fat meal, 21% ↓ mean AUC and 22% ↓ in mean C_{max} observed relative to fasting conditions. However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals.
Protein Binding	98-99% (albumin and AAG)
Vd	0.41 ± 0.25 L/kg
Tmax	2 (fasting), 4 (with food)
serum T ½	3-5 hours

Drug Concentrations	Capsules (600 mg po q12h): • Cmax: 11.2 ± 3.6 ug/mL, Cmin 3.7 ±2.6 ug/mL In vivo intracellular accumulation: cell/plasma ratio 1.0 (range 0.6-2.28). Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, $AUC_{(0-\infty)}$ met equivalence criteria but mean C_{max} was ↑ by 26% (92.8% confidence intervals: ↑15 -↑39%). No information is available comparing tablets to capsules under fasting conditions.
Minimum target trough concentrations (for wildtype virus)	2.1 mg/mL
CSF (% of serum)	CSF concentrations usually < 0.05 mg/L (may have similar unbound drug concentrations as plasma) 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	- metabolic auto-induction occurs in first 2 weeks- dose escalation necessary to avoid overdosing and minimize side-effects Ritonavir is metabolized to 5 major metabolites Ritonavir is the most potent inhibitor of the P450 enzyme system (CYP3A>2D6>2C9>2C19>2A6,2E1). Ritonavir also induces CYP1A2 and glucuronyl transferase activity. May also induce CYP2C9, 2C19. - isopropylthiazole oxidation metabolite(M-2) has activity similar to ritonavir, but conc. are low
Excretion	- 86% biliary/ fecal - 11% renal
Dosing – Adult	-**<u>High dose:</u>** 600 mg po q12h**; for better tolerability, start with 300 mg BID and increase dose at 2 to 3 day intervals by 100mg BID.** **<u>Low dose</u>** (for boosting other PIs): due to intolerance to RTV at high doses, ritonavir is mainly in lower doses as a metabolic booster of other PIs. The dosage varies depending on the respective drug used. See drug interaction tables for more detailed dosing. All formulations (including the tablet) must **be taken with meals**. To improve palatability, mix solution with Ensure or chocolate milk within 1 hour of dosing.
Dosing – Pediatric	<u>For children 1 month-2 years of age:</u> The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily. If

	patients do not tolerate 400 mg/m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. General Pediatric Dosing: 400 mg/m^2/dose po bid range: 350-400 mg/m^2/dose po bid **Initial**: start at 250 mg/m^2/dose & ↑ dose over 5 days: 250 mg/m^2/dose x **2/7** (or ↑ dose by 100 mg cap), then 300 mg/m^2/dose x **2/7**, then 350 mg/m^2/dose **1/7**, then 400 mg/m^2/dose po bid **Neonatal** (≤ 12 hrs postbirth) PACTG 354: *Protocol Dose*: 350 mg/m^2/dose po bid x 4 wks
Special instructions for pediatric patients	When possible, dose should be administered using a calibrated dosing syringe. **Liquid is unpalatable, bad aftertaste** 1) Dull taste buds: give **after** popsicle or frozen juice 2) Give with **fat**: ice cream, high fat yogurt, PC® Devon cream 3) **Coat** mouth: give after grape jelly, maple syrup or peanut butter on toast 4) **Mix** with: formula, milk, chocolate milk, ice cream, pudding, maple syrup, Tang®, Ensure® 5) Give **strong flavour** after dose: maple syrup, cheese, strong-flavoured chewing gum - flush g-tube with milk or enteral feed Avoid co-administration of amprenavir solution with ritonavir solution. A competitive metabolic interaction with propylene glycol contained in amprenavir (550 mg/ml) & ethanol in ritonavir (43% v/v ethanol) may occur. Both are substrates of alcohol dehydrogenase. A ritonavir powder formulation (alcohol and propylene glycol free) is in development. In a randomized, partial crossover study in healthy adult subjects, ritonavir powder formulation in water was bioequivalent to ritonavir oral solution. Ritonavir powder administered in chocolate milk, pudding, infant formula or apple sauce was bioequivalent to the powder formulation administered in water. Compared to fasting conditions, moderate-fat and high-fat meals were associated with ~25-40% and 35-50% reduction in ritonavir concentrations, respectively.[Salem et al. 2014 IWCPHT]
Adjust in Liver Dysfunction	No dosage recommendation available, use with caution in hepatic impairment.
Adjust in Renal Failure/Dialysis	Dosage adjustment not necessary. May administer drug regardless of hemodialysis schedule.
Toxicity	**Most of these toxicities are dose-related. When RTV is used in low doses, the toxicity is decreased.** **GI:** diarrhea, nausea, vomiting ,dyspepsia, abdominal discomfort, anorexia , taste disturbances , dehydration+

	syncope/ hypotension/ renal insufficiency, pancreatitis **Hepatic:** ↑ transaminases >5x (2-15%), jaundice, (↑ risk in HBV/HCV), hepatotoxic fatalities reported Caution in liver failure, liver enzyme abnormalities, or hepatitis **CNS:** perioral & peripheral paresthesias asthenia, headache, fatigue, weakness, light-headedness, seizures **Derm:** Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necroylsis have been reported. **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. Solution contains alcohol.
Pregnancy & Lactation	Pregnancy risk category B. Minimal placental transfer in humans. Low drug levels in pregnancy, therefore use only in low-doses to boost the concentration of other PIs (i.e. saquinavir, indinavir, lopinavir).
Drug Interactions	Ritonavir is the most potent inhibitor of the P450 enzyme system (CYP3A>2D6>2C9>2C19>2A6,2E1). Ritonavir induces CYP1A2 and glucuronyl transferase activity. May also induce CYP2C9, 2C19. Ritonavir inhibits OATP1B1/1B3 as well as the renal transporter MATE1. See Separate Drug Interaction Table. The concomitant administration of ritonavir oral solution with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. or preparations that contain alcohol is contraindicated. Do not coadminister with amprenavir oral solution.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	100mg (white) soft gel capsules; DIN 02241480 100 mg white, film-coated tablets; DIN 02357593, bottles of 30. Capsules contain lecithin and coconut oil. In Canada, ritonavir capsules are exposed to soy lecithin. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy (consult an allergist prior to taking capsules). 80mg/ml oral solution (240ml bottles); DIN 02229145 Both capsules (12%v/v) and solution (43% v/v) contain ethanol.

Storage	Solution stable at room temperature and should be used by product expiration date. Capsules should be refrigerated until dispensed, then stable for 30 days at room temperature. – photosensitive. Tablets may be stored at room temperature; exposure to high humidity outside the original container for longer than 2 weeks is not recommended.

References:

Abbott Laboratories, Ltd. Norvir® Product Monograph. St. Laurent, QC, November 28, 2011.

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

Izzedine H, Launay-Vacher V, Deray G. Pharmacokinetics of ritonavir and nevirapine in peritoneal dialysis. Nephrol Dial Transplant. 2001 Mar;16(3):643.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Salem AH, Chiu Y, Valdes JM, Nilius AM, Klein CE. A novel ritonavir pediatric powder formulation is bioequivalent to Norvir oral solution with a similar food effect [abstract P_01]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, Washington DC, May 19-22, 2014.