**Selected Properties of Atazanavir**

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| **Other names** | BMS 232632, Reyataz®<br><br>Combination formulation:<br><br>• Atazanavir 300 mg/cobistat 150 mg (Evotaz®) |
| **Manufacturer** | Bristol-Myers Squibb Canada |
| **Pharmacology/Mechanism of Action** | Atazanavir is an azapeptide HIV–1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV–1 infected cells, thus preventing formation of mature virions. |
| **Activity** | Atazanavir exhibits anti-HIV–1 activity with a mean 50% effective concentration (EC50) in the absence of human serum of 2-5 nM against a variety of laboratory and clinical HIV–1 isolates. Atazanavir has additive in vitro antiviral activity with the protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and NRTIs (didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) without enhanced cytotoxicity. |
| **Resistance - genotypic** | Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations):<br><br>Major: I50L, *I84V#,* N88S<br>Minor: *L10I/F/V#, G16E#,* K20R/M/I, L24I, V32I, *L33I/F/V#*, M36I/L/V, *M46I/L#,* G48V, I54L/V/M/T, *D60E#*, I62V, A71V/I/T/L, G73C/S/T/A, V82A/T, *I85V#*, L90M, I93L<br>**as major & minor mutations accumulate, susceptibility to PIs decreases*<br><br>*#presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M is present* |
| **Resistance - phenotypic** | Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):<br>I50L: 6-fold ↑ (intermediate-to-high level resistance)<br>I84V + L90M: 10-fold ↑ (high level resistance) |
| **Cross-Resistance** | Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects indicate:<br>• the I50L and I50V substitutions yield selective resistance to atazanavir and amprenavir, respectively, and do not appear to confer cross-resistance.<br>• other atazanavir-resistant isolates are highly cross-resistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir).<br>• a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors. |
| **Oral Bioavailability** | Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir if antacids, buffered |

<table>
<tr><td></td><td>medications, H2-receptor antagonists, and proton-pump inhibitors are administrated with atazanavir. Avoid concomitant use (kinetic study showed significantly reduced atazanavir exposure when coadministered with omeprazole; atazanavir absorption did not improve when given either boosted with ritonavir or with 8 oz cola).</td></tr>
<tr><td>Effect of Food</td><td>Administration of atazanavir and atazanavir/ritonavir with food enhances bioavailability (35-70% ↑ AUC) and reduces pharmacokinetic variability by 50%.(Giguere et al. 2010).</td></tr>
<tr><td>Protein Binding</td><td>86%, binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).</td></tr>
<tr><td>Vd</td><td></td></tr>
<tr><td>Tmax</td><td>2-2.5 hours</td></tr>
<tr><td>serum T ½</td><td>Approximately 7 hours</td></tr>
<tr><td>Drug Concentrations</td><td>Steady-state atazanavir concentrations in HIV-positive subjects after 400 mg QD administration with food:<br>Cmax 3152 ng/mL, Cmin 273 ng/mL, AUC 22262 ng.h/mL<br><br>Atazanavir plasma concentrations after 300/100 mg ritonavir QD: Cmax 5233 ng/mL, Cmin 862 ng/mL, AUC 53761 ng.h/mL<br><br>Atazanavir administered in a fixed-dose tablet (300 mg atazanavir/150 mg cobicistat) demonstrated bioequivalence to coadministration of the individual components when given with a light meal in healthy adult subjects.[Tao et al. 2014]<br><br>10 HIV positive patients on ATV 400mg daily switched to ATV 200mg BID, atazanavir kinetics assessed at baseline and after 10 days of BID regimen. Atazanavir 200mg BID led to higher plasma Ctrough, lower Cmax and similar AUC compared to standard ATV 400mg daily dose.(Bonora et al. 2008; Gonzalez de Requena, 2010.)
<table>
<tr><td>Mean plasma levels</td><td>ATV 400 mg daily (Baseline)</td><td>ATV 200 mg BID</td><td>Mean plasma GM ratios (ATV 200 BID:ATV 400 mg QD)</td></tr>
<tr><td>Ctrough</td><td>138 ng/ml</td><td>305 ng/mL</td><td>2.19</td></tr>
<tr><td>Cmax</td><td>2786 ng/ml</td><td>1314 ng/mL</td><td>0.48</td></tr>
<tr><td>AUC24h</td><td>20780 ng/ml.h</td><td>16904 ng/ml.h</td><td>0.8</td></tr>
<tr><td>Mean intracellular levels</td><td>ATV 400 mg daily (Baseline)</td><td>ATV 200 mg BID</td><td>Mean intracellular GM ratios (ATV 200 BID:ATV 400 mg QD)</td></tr>
<tr><td>Ctrough</td><td>465 ng/ml</td><td></td><td>2.93</td></tr>
<tr><td>Cmax</td><td>4058 ng/ml</td><td></td><td>1.27</td></tr>
<tr><td>AUC24h</td><td>35958 ng/ml.h</td><td></td><td>1.51</td></tr>
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Increased bilirubin levels with BID regimen not clinically important. Atazanavir accumulates within the cell to a slightly greater extent versus plasma.

Open label, prospective, single center study to investigate kinetics of lower dose ATV/r. 22 Thai HIV infected adult patients suppressed on ATV/r 300mg/100mg daily were changed to **200mg/100mg daily** (7 pts were also on TDF).

| Median (+IQR) | ATV/r 300/100mg at baseline | ATV/r 200mg/100mg at day 14 | p |
|---|---|---|---|
| AUC 0-12hr | 65.4 mg/L.h | 35.5 mg/L.h | <0.001 |
| Cmax | 6.1 mg/L | 3.9 mg/L | <0.001 |
| Cmin | 1 mg/L | 0.5 mg/L | <0.001 |

No patients had subtherapeutic levels (<0.15mg/L). (Gorowara M et al. 2008). Results of ATV/r 200/100mg daily in Thai subjects comparable to Caucasian population on standard dose (Burger et al AAC, 2006).

In 29 HIV-infected patients receiving atazanavir-based therapy (14 unboosted, 15 boosted), median intracellular atazanavir Ctrough concentrations were higher for boosted vs. unboosted atazanavir, and intracellular concentrations were higher than median plasma Ctrough:

| | Unboosted ATV | Boosted ATV | p |
|---|---|---|---|
| Plasma Ctrough (ng/mL) | 132 (111-184) | 543 (393-1081) | |
| Intracellular Ctrough (ng/mL) | 328 (168-440) | 1032 (819-3091) | 0.001 |
| | P=0.001 | P=0.005 | |

(Siccardi et al. 2010)

In 416 HIV-positive subjects on atazanavir-based regimens, routine atazanavir Ctrough was not significantly different between **smokers (n=246) and non-/ex-smokers (n=170)**.[Guillemi et al. 2010]. In healthy subjects taking either atazanavir or atazanavir/ritonavir, moderate tobacco use (up to 10 cigarettes per day) was not associated with a significant difference in atazanavir pharmacokinetics.[Blonk et al. 2011]

In 18 HIV-infected **women** on ≥ 6 months of cART (tenofovir, emtricitabine, atazanavir, and ritonovir) with plasma viral loads < 50 copies/mL, blood and cervicovaginal samples were collected twice weekly for three weeks following menses. The ratio of cervicovaginal to plasma drug concentrations (geometric mean) was 11.6 for emtricitabine (CI 8.1-16.6), 3.18 for tenofovir (CI 1.94-5.21), 2.59 for atazanavir (CI 1.81-3.71), and 1.52 for ritonavir (CI 1.04-2.23). HIV-1 RNA was detected in 14 cervicovaginal samples (13.7%, CI 7.7%-24.1%) from 8 (44%) women; all virus-positive samples had virus loads < 500 copies/10 mL CVL.[Sheth et al. IAS 2011]

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| | Atazanavir total and unbound concentrations were measured in HIV-positive subjects with **compensated cirrhosis** (n=8, median MELD 11, Child score A, n=7 or B n=1) and HIV-positive subjects without hepatic disease (n=3). In patients with compensated cirrhosis, total and unbound atazanavir concentrations were similar to controls and historical data.[Curran et al. 2013]<br><br>A case report of a 37 year old HIV/HCV coinfected male (60 kg) who **ingested 8700 mg atazanavir** without ritonavir; last ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48 hours post-overdose; values returned to baseline at one-month follow-up. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012] |
| **Minimum target trough concentrations (for wildtype virus)** | Median wild-type EC90 = 14 ng/mL<br>Suggested minimum trough: 150 ng/mL. |
| **CSF (% of serum)** | In 4 HIV-positive subjects dosed with atazanavir 400 mg QD for 12 weeks, the cerebrospinal fluid/plasma ratio ranged between 0.0021 and 0.0226.<br><br>In 26 participants receiving atazanavir 300/ritonavir 100 mg QD, ATV concentrations in the CSF were highly variable, and were 100-fold lower than plasma concentrations. 17 (65%) CSF samples were >11 ng/mL (ATV IC50 for WT) [Best et al. CROI 2006].<br><br>2010 CNS Penetration Effectiveness (CPE) Score: 2 (boosted and unboosted atazanavir)<br>[Letendre S et al. 2010] |
| **Metabolism** | Extensively metabolized by CYP3A4. Atazanavir inhibits CYP3A and UGT1A1 at clinically relevant concentrations. Atazanavir is a weak inhibitor of CYP2C8. Caution when unboosted atazanavir is coadministered with drugs that are 2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir.<br><br>Atazanavir does not inhibit CYP2C19 or CYP2E1 at clinically relevant concentrations. |
| **Excretion** | Approximately 7% excreted unchanged in the urine.<br><br>47 HIV-positive patients treated with ATV containing regimens were tested to determine if ABCB1 and CYP3A5 polymorphisms are associated with ATV concentrations and/or immunological responses.<br>• ABCB1 haplotype (3435CT-2677GT) was significantly associated with faster ATV oral clearance than 3435CC-2677GG (mean 12.79 VS 7.3L/hr, p=0.018). Trend for ↑ clearance observed in C3435T and G2677T variant carriers<br>• Mean CD4 counts were 375 for ABCB1 2677GG and 547 for 2677GT (p=0.036) |

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<tr><td></td><td>
<ul><li>No relationships were identified with CYP 3A5</li></ul>
Authors state these pilot data provide rationale for the development of individualized ATV regimens [Ma et al. ICAAC 2007].
</td></tr>
<tr><td>Dosing – Adult</td><td>
<table>
<tr><th colspan="3">Recommended Atazanavir and Ritonavir Dosage in Adults</th></tr>
<tr><th></th><th>Atazanavir Once Daily Dosage</th><th>Ritonavir Once Daily Dosage</th></tr>
<tr><td colspan="3">Treatment-Naive Adult Patients</td></tr>
<tr><td>recommended regimen</td><td>300 mg</td><td>100 mg</td></tr>
<tr><td>unable to tolerate ritonavir</td><td>400 mg</td><td>N/A</td></tr>
<tr><td>in combination with efavirenz</td><td>400 mg</td><td>100 mg</td></tr>
<tr><td colspan="3">Treatment-Experienced Adult Patients</td></tr>
<tr><td>recommended regimen</td><td>300 mg</td><td>100 mg</td></tr>
<tr><td>in combination with both H2RA and tenofovir</td><td>400 mg</td><td>100 mg</td></tr>
<tr><td colspan="3">Recommended Dosage of Atazanavir and Ritonavir in Pregnant Patients</td></tr>
<tr><th></th><th>Atazanavir Once Daily Dosage</th><th>Ritonavir Once Daily Dosage</th></tr>
<tr><td colspan="3">Treatment-Naive and Treatment-Experienced</td></tr>
<tr><td>Recommended Regimen</td><td>300 mg</td><td>100 mg</td></tr>
<tr><td colspan="3">Treatment-Experienced During the Second or Third Trimester When Coadministered with either H2RA or Tenofovir</td></tr>
<tr><td>In combination with either H2RA or tenofovir</td><td>400 mg</td><td>100 mg</td></tr>
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</td></tr>
<tr><td>Dosing – Pediatric</td><td>
Should not be administered to infants < 3 months due to risk of kernicterus (a type of brain damage caused by excessive levels of bilirubin).<br><br>
<u>Dosing for atazanavir capsules</u>:<br><br>
The recommended dosage of atazanavir for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dosage.<br><br>
Atazanavir capsules must be taken with food.
<table>
<tr><th colspan="3">Recommended Dosage of Atazanavir Capsules and Ritonavir in Pediatric Patients (6 to <18 years of age)</th></tr>
<tr><th>Body weight</th><th>Atazanavir Daily Dosage</th><th>Ritonavir Daily Dosage</th></tr>
<tr><td colspan="3">Treatment-Naive and Treatment-Experienced</td></tr>
<tr><td>Less than 15 kg</td><td>Capsules not recommended</td><td>N/A</td></tr>
<tr><td>15 kg to <20 kg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>20 kg to <40 kg</td><td>200 mg</td><td>100 mg</td></tr>
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| | <table><tr><td>At least 40 kg</td><td>300 mg</td><td>100 mg</td></tr><tr><td colspan="3">Treatment-Naive, at least 13 years old and cannot tolerate ritonavir</td></tr><tr><td>At least 40 kg</td><td>400 mg</td><td>N/A</td></tr></table><br><br><u>Dosing for atazanavir oral powder</u>:<br><br>Atazanavir oral powder is indicated for treatment-naive or treatment-experienced pediatric patients at least 3 months of age and weighing at least 10 kg and less than 25 kg. Atazanavir oral powder must be mixed with food or beverage for administration and ritonavir must be given immediately afterwards.<br><br>Recommended Dosage of Atazanavir Oral Powder and Ritonavir in Pediatric Patients (at least 3 months of age and weighing at least 10 kg and less than 25 kg):<br><table><tr><th>Body Weight</th><th>Daily Dosage of Atazanavir Oral Powder</th><th>Daily Dosage of Ritonavir Oral Solution</th></tr><tr><td>10 kg to <15 kg</td><td>200 mg (4 packets)[b]</td><td>80 mg</td></tr><tr><td>15 kg to<25 kg</td><td>250 mg (5 packets)[b]</td><td>80 mg</td></tr></table> |
| **Special instructions for pediatric patients** | Oral powder may be mixed with minimum 15 mL of applesauce, or yogurt, or 30 mL of milk or water (administer within 1 hour of mixing). Do not mix with juices or foods with high pH. Administer ritonavir dose immediately following atazanavir.<br><br>In an open label, multicentre study of atazanavir and atazanavir/ritonavir in children 91 days-21 years, the pharmacokinetics of atazanavir capsules and atazanavir orange-vanilla flavoured powder were studied. Day 7 atazanavir kinetics were compared in children of similar age receiving powder vs. capsules; the powder was found to be 40% less bioavailable at the same BSA-based dose. Therefore, suggest converting from powder to capsule by multiplying the powder dose by 0.6 and rounding up to the nearest 50 mg.[Kiser J et al. 2011]<br><br>**<u>Atazanavir capsules</u>** may be opened and the contents mixed with applesauce for immediate ingestion with a light meal. In-house study showed that the bioavailability of the contents of two 200-mg atazanavir capsules mixed with applesauce was 91.7% relative to atazanavir capsules taken intact. In addition, administration of the contents of two 200-mg capsules was well tolerated (Bristol Myers Squibb, Personal Communication, October 22, 2008). |
| **Adjust in Liver Dysfunction** | In adults with moderate to severe hepatic impairment (Child-Pugh B and C), mean atazanavir AUC after a single 400 mg dose was 42% greater than in healthy volunteers, while the mean half-life was 12.1 hours compared to 6.4 hours.<br>The following dosage adjustments are recommended:<br>Child-Pugh Score 7-9: 300 mg QD |

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| | Child-Pugh score >9: not recommended<br><br>In a cohort of HIV/HCV coinfected patients on stable atazanavir 400 mg QD, median atazanavir Ctrough was 0.60 ug/mL vs. 0.24 ug/mL in HIV+/HCV- patients, p<0.001. Median atazanavir Ctrough with ATV 300/rtv 100 mg QD was not statistically different between the groups (0.70 vs. 0.73 ug/mL, respectively).[Regazzi et al. 2009] |
| **Adjust in Renal Failure/Dialysis** | In an open-label study in HIV-negative participants, steady-state kinetics of atazanavir 400 mg QD were compared between renally impaired (Clcr<30 mL/min) and non-renally impaired (Clcr>80 mL/min) subjects. Compared to controls, atazanavir AUC ↑ 19% and Cmin ↑ 96% in the renally impaired group. No dosage adjustment of atazanavir is necessary in renal impairment not managed with hemodialysis.[Agarwala et al. 2007]<br><br>In subjects on hemodialysis, atazanavir exposures were ↓ 25-40% compared to non-renally impaired controls; atazanavir exposures were decreased independent of time of administration in relation to dialysis. Atazanavir dialysis clearance was low, with 2.1% of the administered dose eliminated over a 4 hour dialysis period. May wish to consider boosted atazanavir (300 mg/ritonavir 100 mg QD) in hemodialysis patients.[Agarwala et al. 2007]<br><br><u>Atazanavir (Reyataz) Monograph</u>:<br>For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for atazanavir. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive atazanavir 300 mg with ritonavir 100 mg. <u>Atazanavir should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis</u> |
| **Toxicity** | Skin rash (21%), < 1% severe rash; asymptomatic indirect hyperbilirubinemia (30%), jaundice (10%), headache, fever, arthralgias, depression, insomnia, dizziness, nausea/vomiting/diarrhea, paresthesias, prolongation of PR interval of EKG.<br><br>Protease class effects include: hyperlipidemia & hypertriglyceridemia (except atazanavir), hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.<br><br>Kidney Stones (uncommon)<br>• American Reports: 30 cases ATV associated nephrolithiasis recorded between Dec 2002 to Jan 2007 in the US FDA Adverse Event Reporting System Database (Voluntary reporting)<br>• French Case Series: 11/1134 patients developed ATV nephrolithiasis (Mar 2004 – Feb 2007). 4 pts had history of kidney stones before ATV exposure. Mean onset for ADR ~ 23 months. 1/6 patients that were kept on ATV developed |

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| | recurrent kidney stones despite instructions to drink more fluids, including acidic beverages such as cola.<br>• Reports suggest kidney stones composed of 60-100% ATV crystals<br>• Exact mechanism for ADR is unknown.<br>• 7% of the ATV dose is excreted unchanged in the urine. Like IDV, the solubility of ATV is increased in acid fluids<br>Risk Factors: not drinking enough fluid, having urine that is not acidic, having a history of kidney stones.<br><br>A case report of a 37 year old HIV/HCV coinfected male (60 kg) who ingested 8700 mg atazanavir without ritonavir; last ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48 hours post-overdose; values returned to baseline at one-month follow-up. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012] |
| **Pregnancy & Lactation** | Pregnancy risk category B. No experience in human pregnancy. Theoretical risk with indirect hyperbilirubinemia which may be additive with neonatal elevations in bilirubin. Placental passage unknown, however it has been low with other PIs.<br><br>Atazanavir exceeded the IC50wt in plasma, breast milk and vaginal secretions. Median percentage of plasma concentrations was 7.3% (day 5 breast milk), 7.9% (day 14 breast milk) and 4.8% (vaginal secretions).[Neely et al. 2009]<br><br>In 6 HIV-infected pregnant women receiving atazanavir (all VL<40 copies/mL at delivery), mean atazanavir cord:mother blood concentration ratio was 0.18 (SD +/- 0.11); cord blood concentrations were below cut-off values in 2 (33.3%) of samples. Mean amniotic fluid:maternal plasma ratio for lopinavir was 0.25. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].<br><br>In a prospective study of atazanavir PK in pregnancy (with or without tenofovir), women received ATV 300/100 mg QD during the 2nd trimester, ATV 400/100 mg QD during the 3rd trimester, and 300/100 mg QD post-partum. Atazanavir exposures were low in the 2nd trimester but improved in the 3rd trimester with the dose increase. The median ATV cord blood concentration was 0.22 ug/mL and median cord blood:maternal plasma ratio was 0.18. ATV 400/100 mg QD provides adequate ATV exposure during the 3rd trimester and should be considered during the 2nd trimester as well.[Mirochnick et al. 2011; Kreitchmann et al. 2013]<br><br>Maternal and cord atazanavir concentrations were measured in 15 mother-baby pairs. Detectable atazanavir concentrations were present in 12/15 cord samples (median 223 ng/mL, range <48-531), with 8/12 > MEC of 150 ng/mL. There was a significant correlation between maternal blood and cord blood atazanavir concentrations (R2=0.632, p<0.001). The mean maternal:cord blood ratio was 0.14 (95%CI 0.08-0.20). There |

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| | was no correlation between atazanavir exposures and bilirubin concentrations, no cases of hyperbilirubinemia were noted.[Lambert et al. 2013] |
| **Drug Interactions** | Avoid concomitant administration with antacids, proton-pump inhibitors, or H2-blockers, as atazanavir absorption is significantly compromised.<br><br>Atazanavir is an inhibitor of CYP3A and UGT1A1. Atazanavir is a weak inhibitor of CYP2C8. With boosted atazanavir, ritonavir appears to induce CYP2C8 and offset inhibition by ATV.(Sevinsky et al. 2008)<br><br>See separate Drug Interaction Table for more information. |
| **Baseline Assessment** | Assess risk factors for diabetes, coronary artery disease (less with ATV), 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** | *Oral powder, 50 g per packet, available in U.S.*<br>*100 mg capsules (blue/white) available in U.S.*<br>150 mg capsules (blue/powder blue); DIN 02248610<br>200 mg capsules (blue/blue); DIN 02248611<br>300 mg capsules (blue/red); DIN 02294176<br><br>Combination formulation:<br>*300 mg atazanavir/150 mg cobicistat tablet (available in U.S.)* |
| **Storage** | Store at room temperature. |

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