℞ ATAZANAVIR
ATAVIR 150/200/300
150 mg, 200 mg and 300 mg Capsule
Protease Inhibitor
2055783

11151

℞ **ATAZANAVIR**
ATAVIR 150/200/300
150 mg, 200 mg and 300 mg Capsule
Protease Inhibitor

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ATAZANAVIR CAPSULES safely and effectively. See full prescribing information for ATAZANAVIR CAPSULES.
ATAZANAVIR capsules, for oral use
Initial U.S. Approval: 2003

Description

Atazanavir 150mg Off white to pale yellow colored granular powder filled in size 1 hard gelatin capsules with Green Opaque cap imprinted with "H" in black color and Light Green opaque Body imprinted with "A6" in black colour.

Atazanavir 200mg Off white to pale yellow colored granular powder filled in size 0 hard gelatin capsules with Green Opaque cap imprinted with "H" in black color and Light Green opaque Body imprinted with "A7" in black colour.

Atazanavir 300mg Off white to pale yellow colored granular powder filled in size 00 hard gelatin capsules with orange Opaque cap imprinted with "H" in black color and Green opaque Body imprinted with "A8" in black colour.

RECENT MAJOR CHANGES

Dosage and Administration, Testing Prior to Initiation and During Treatment with atazanavir capsules (2.2)	10/2017
Dosage of Atazanavir Capsules in Pediatric Patients (2.4)	05/2017
Contraindications (4)	03/2018
Warnings and Precautions Chronic Kidney Disease (5.5)	10/2017

INDICATIONS AND USAGE

Atazanavir capsules are a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 6 years and older weighing at least 15 kg. (1)

DOSAGE AND ADMINISTRATION

- *Pretreatment testing:* Renal laboratory testing should be performed in all patients prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules. Hepatic testing should be performed in patients with underlying liver disease prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules. (2.2)
- *Treatment-naive adults:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food or atazanavir 400 mg once daily with food. (2.3)
- *Treatment-experienced adults:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food. (2.3)
- *Pediatric patients:* Atazanavir capsule dosage is based on body weight not to exceed the adult dose and must be taken with food. (2.4)
- *Pregnancy:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food, with dosing modifications for some concomitant medications. (2.6)
- *Dosing modifications:* may be required for concomitant therapy (2.3, 2.4, 2.6), renal impairment (2.7), and hepatic impairment (2.8).

DOSAGE FORMS AND STRENGTHS

- Capsules: 150 mg, 200 mg, 300 mg. (3, 16)

CONTRAINDICATIONS

- Atazanavir capsules are contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)

[illegible]

FULL PRESCRIBING INFORMATION: CONTENTS*

[illegible]

℞ **ATAZANAVIR**
ATAVIR 150/200/300
150 mg, 200 mg and 300 mg Capsule
Protease Inhibitor

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with atazanavir capsules. For more information, see "Who should not take atazanavir capsules?" and "What should I tell my healthcare provider before taking atazanavir capsules?"

What are atazanavir capsules?

Atazanavir capsules is a prescription HIV-1 (Human Immunodeficiency Virus-type 1) medicine that is used with other antiretroviral medicines to treat HIV-1 infection in adults and children 3 months of age and older and who weigh at least 11 pounds (5 kg). HIV-1 is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

Atazanavir capsules should not be used in children younger than 3 months of age.

When used with other antiretroviral medicines to treat HIV-1 infection, Atazanavir capsules may help:

- reduce the amount of HIV-1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

Atazanavir capsules does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Who should not take atazanavir capsules?
Do not take atazanavir capsules if you:

- are allergic to atazanavir capsules or any of the ingredients in atazanavir capsules. See the end of this leaflet for a complete list of ingredients in atazanavir capsules.
- are taking any of the following medicines. Taking atazanavir capsules with these medicines may affect how atazanavir capsules works. Atazanavir capsules may cause serious life-threatening side effects or death when used with these medicines:
  - o alfuzosin (UROXATRAL®)
  - o cisapride (PROPULSID®)
  - o elbasvir/grazoprevir (ZEPATIER®)
  - o ergot medicines including:
  - • ergotamine tartrate (CAFERGOT®, MIGERGOT®, ERGOMAR®, ERGOSTAT®, MEDIHALER®, Ergotamine, WIGRAINE®, WIGRETTES®)
  - • dihydroergotamine mesylate (D.H.E. 45®, MIGRANAL®)
  - • methylergonovine (METHERGINE®)
  - o glecaprevir/pibrentasvir (MAVYRET®)
  - o indinavir (CRIXIVAN®)
  - o irinotecan (CAMPTOSAR®)
  - o lovastatin (ADVICOR®, ALTOPREV®, MEVACOR®)
  - o midazolam (VERSED®), when taken by mouth for sedation
  - o nevirapine (VIRAMUNE®, VIRAMUNE XR®)
  - o pimozide (ORAP®)
  - o rifampin (RIFADIN®, RIFAMATE®, RIFATER®, RIMACTANE®)
  - o sildenafil (REVATIO®), when used for the treatment of pulmonary arterial hypertension
  - o simvastatin (SIMCOR®, VYTORIN®,ZOCOR®)
  - o St. John's wort (*Hypericum perforatum*)
  - o lurasidone (LATUDA®) if atazanavir is used with ritonavir (NORVIR®)
  - o triazolam (HALCION®)

Serious problems can happen if you or your child takes any of the medicines listed above with atazanavir capsules.

What should I tell my healthcare provider before taking atazanavir capsules?
Before taking atazanavir capsules, tell your healthcare provider if you:

- have heart problems
- have liver problems, including hepatitis B or C virus infection
- are receiving dialysis treatment
- have diabetes
- have hemophilia
- have any other medical conditions
- are pregnant or plan to become pregnant. Talk to your healthcare provider about taking atazanavir capsules during your pregnancy or if you are planning to become pregnant while you are taking atazanavir capsules.
  - o **Hormonal forms of birth control, such as injections, vaginal rings or implants, contraceptive patch, and some birth control pills may not work during treatment with atazanavir capsules.** Talk to your healthcare provider about forms of birth control that may be used during treatment with atazanavir capsules.
  - o **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
  - o **After your baby is born,** tell your healthcare provider if your baby's skin or the white part of the eyes turns yellow.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you are taking atazanavir capsules**. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Atazanavir capsules can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with atazanavir capsules. **Keep a list of your medicines to show your healthcare provider and pharmacist.** You can ask your healthcare provider or pharmacist for a list of medicines that interact with atazanavir capsules. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take atazanavir with other medicines.

How should I take atazanavir capsules?

- **Take atazanavir capsules exactly as your healthcare provider tells you to**.
- Do not change your dose or stop taking atazanavir capsules unless your healthcare provider tells you to.
- Stay under the care of your healthcare provider during treatment with atazanavir capsules.
- Atazanavir capsules must be used with other antiretroviral medicines.
- Take atazanavir capsules 1 time each day.
- Take atazanavir capsules with food.
- Swallow the capsules whole. Do not open the capsules.
- If you miss a dose of atazanavir capsules, take it as soon as you remember. Then take the next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much atazanavir capsules, call your healthcare provider or go to the nearest hospital emergency room right away.

When your supply of atazanavir capsules starts to run low, get more from your healthcare provider or pharmacy. It is important not to run out of atazanavir capsules. The amount of HIV-1 in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to atazanavir capsules and harder to treat.

What are the possible side effects of atazanavir capsules?
Atazanavir capsules can cause serious side effects, including:

- **A change in the way your heart beats (heart rhythm change).** Tell your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **Skin rash.** Skin rash is common with atazanavir capsules but can sometimes be severe. Skin rash usually goes away within 2 weeks without any change in treatment. Severe rash may develop in association with other symptoms which could be serious. If you develop a severe rash or a rash with any of the following symptoms, stop taking atazanavir capsules and call your healthcare provider right away:
  - o general feeling of discomfort or "flu- like" symptoms
  - o fever
  - o muscle or joint aches
  - o red or inflamed eyes, like "pink eye" (conjunctivitis)
  - o blisters
  - o mouth sores
  - o swelling of your face
  - o painful, warm, or red lump under your skin
- **Yellowing of your skin or the white part of your eyes** is common with atazanavir capsules, and is usually not harmful in adults and infants older than 3 months of age; but it could also be a symptom of a serious problem. These effects may be due to increases in bilirubin levels in your blood (bilirubin is made by the liver). Although these effects may not be damaging to your liver, skin, or eyes, tell your healthcare provider right away if your skin or the white part of your eyes turns yellow.
- **Liver problems.** If you have liver problems, including hepatitis B or C infection, your liver problems may get worse when you take atazanavir capsules. Your healthcare provider will do blood tests to check your liver before you start atazanavir capsules and during treatment. Tell your healthcare provider right away if you get any of the following symptoms:
  - o dark "tea-colored" urine
  - o your skin or the white part of your eyes turns yellow
  - o light colored stools
  - o nausea
  - o itching
  - o stomach-area pain
- **Chronic kidney disease.** Atazanavir capsules may affect how well your kidneys work. Your healthcare provider will do blood and urine tests to check your kidneys before you start atazanavir and during treatment.
- **Kidney stones** have happened in some people who take atazanavir capsules. Tell your healthcare provider right away if you get symptoms of kidney stones which may include, pain in your low back or low stomach-area, blood in your urine, or pain when you urinate.
- **Gallbladder problems** have happened in some people who take atazanavir capsules. Tell your healthcare provider right

Dimensions: 500 x 830 mm
Book Fold: 50x70 mm
Printed on 40 GSM Bible Paper, Front & Back Printing
Colour: 1 (Black)

11151 11152

away if you get symptoms of gallbladder problems which may include:

- o pain in the right or middle upper stomach area
- o fever
- o nausea and vomiting
- o your skin or the white part of your eyes turns yellow

- **Diabetes and high blood sugar (hyperglycemia)** have happened or have worsened in some people who take protease inhibitor medicines like atazanavir capsules. Some people have had to start taking medicine to treat diabetes or have had to change their diabetes medicine.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting atazanavir capsules.
- **Changes in body fat** can happen in people taking HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding problems in people with hemophilia** have happened when taking protease inhibitors like atazanavir capsules.

The most common side effects of atazanavir capsules include:

- nausea
- headache
- stomach-area pain
- vomiting
- trouble sleeping
- numbness, tingling, or burning of hands or feet
- dizziness
- muscle pain
- diarrhea
- diarrhea
- depression
- fever

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of atazanavir capsules. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store atazanavir capsules?

- Store below 30°C.
- Keep capsules in a tightly closed container.

Keep atazanavir capsules and all medicines out of the reach of children.

General information about the safe and effective use of atazanavir capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use atazanavir capsules for a condition for which it was not prescribed. Do not give atazanavir capsules to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about atazanavir capsules that is written for health professionals.

For more information, call 1-866-495-1995.

What are the ingredients in atazanavir capsules?
Active ingredient: atazanavir sulfate
Inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue 1, iron oxide yellow, titanium dioxide, In addition 150 mg capsule shell contains iron oxide black, 200 mg and 300 mg contains FD&C Yellow 6, 300 mg also contains FD&C Red 3. The capsules are printed with black ink containing iron oxide black, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, titanium dioxide.

The brands listed are the trademarks of their respective owners and are not trademarks of Hetero Labs Limited.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
HETERO **HETERO LABS LIMITED**
Unit-III, 22-110, I.D.A., Jeedimetla,
Hyderabad, Telangana state,
INDIA.

The safety, pharmacokinetic profile, and virologic response of atazanavir in pediatric patients at least 3 months of age and older weighing at least 5 kg were established in three open-label, multicenter clinical trials: PACTG 1020A, AI424-451, and AI424-397 [*see Clinical Pharmacology (12.3) and Clinical Studies (14.3)*]. The safety profile in pediatric patients was generally similar to that observed in adults [*see Adverse Reactions (6.1)*]. See *Dosage and Administration (2.4, 2.5)* for dosing recommendations for the use of atazanavir capsules.

8.5 Geriatric Use
Clinical studies of atazanavir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Based on a comparison of mean single-dose pharmacokinetic values for C_{max} and AUC, a dose adjustment based upon age is not recommended. In general, appropriate caution should be exercised in the administration and monitoring of atazanavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Age/Gender
A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18 to 40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically significant pharmacokinetic differences observed due to age or gender.

8.7 Impaired Renal Function
Atazanavir is not recommended for use in HIV-treatment-experienced patients with end-stage renal disease managed with hemodialysis [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

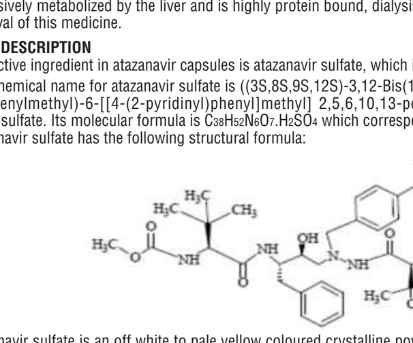
8.8 Impaired Hepatic Function
Atazanavir is not recommended for use in patients with severe hepatic impairment. Atazanavir /ritonavir is not recommended in patients with any degree of hepatic impairment [*see Dosage and Administration (2.8) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE
Human experience of acute overdose with atazanavir is limited. Single doses up to 1,200 mg (three times the 400 mg maximum recommended dose) have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in an HIV-infected patient (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At atazanavir doses resulting in high atazanavir exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed [*see Warnings and Precautions (5.1, 5.8) and Clinical Pharmacology (12.2)*].

Treatment of overdosage with atazanavir should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with atazanavir. Since atazanavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

11 DESCRIPTION
The active ingredient in atazanavir capsules is atazanavir sulfate, which is an HIV-1 protease inhibitor.

The chemical name for atazanavir sulfate is ((3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl] 2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate. Its molecular formula is $C_{38}H_{52}N_6O_7.H_2SO_4$ which corresponds to a molecular weight of 802.9 Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is an off white to pale yellow coloured crystalline powder. Freely soluble in methanol, soluble in dimethylformamide and dimethylsulfoxide.

Atazanavir capsules are available for oral administration in strengths of 150 mg, 200 mg, or 300 mg of atazanavir, which are equivalent to 170.854 mg, 227.805 mg, or 341.708 mg of atazanavir sulfate, respectively. The capsules also contain the following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue 1, iron oxide yellow, titanium dioxide, In addition 150 mg capsule shell contains iron oxide black, 200 mg and 300 mg contains FD&C Yellow 6, 300 mg also contains FD&C Red 3. The capsules are printed with black ink containing iron oxide black, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Atazanavir is an HIV-1 antiretroviral drug [*see Microbiology (12.4)*].

12.2 Pharmacodynamics
Cardiac Electrophysiology
Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram [*see Warnings and Precautions (5.1)*].

Electrocardiographic effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg (maximum recommended dosage) and 800 mg (twice the maximum recommended dosage) were compared with placebo; there was no concentration- dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1,793 HIV- infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval >500 msec [*see Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics
The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV- infected patients after administration of atazanavir 400 mg once daily and after administration of atazanavir 300 mg with ritonavir 100 mg once daily (see Table 17).

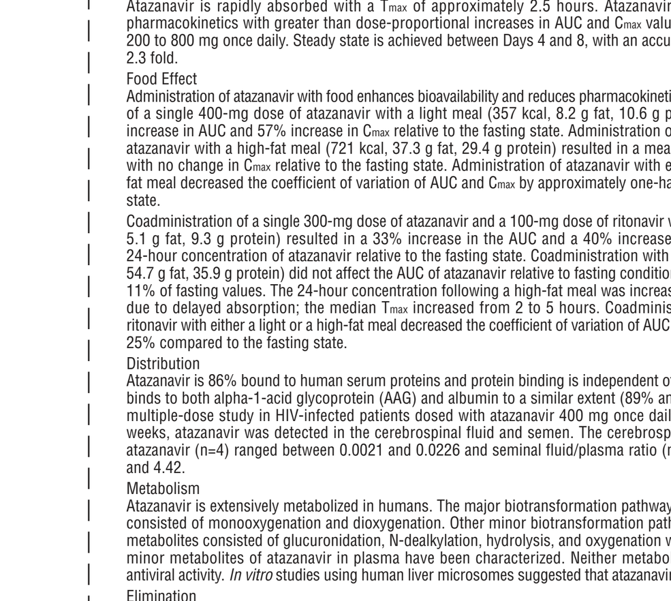
Table 17: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

Parameter	400 mg once daily: Healthy Subjects (n=14)	400 mg once daily: HIV-Infected Patients (n=13)	300 mg with ritonavir 100 mg once daily: Healthy Subjects (n=28)	300 mg with ritonavir 100 mg once daily: HIV-Infected Patients (n=10)
C_{max} (ng/mL) Geometric mean (CV%)	5,199 (26)	2,298(71)	6,129(31)	4,422(58)
Mean (SD)	5,358(1,371)	3,152(2,231)	6,450(2,031)	5,233(3,033)
T_{max} (h) Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28,132(28)	14,874(91)	57,039(37)	46,073(66)
Mean (SD)	29,303(8,263)	22,262(20,159)	61,435(22,911)	53,761(35,294)
T-half (h)				
Mean (SD)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)				
Geometric mean (CV%)	159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298)[b]	1441 (757)	862 (838)

[a] n=26.
[b] n=12.

Figure 1 displays the mean plasma concentrations of atazanavir at steady state after atazanavir 400 mg once daily (as two 200 mg capsules) with a light meal and after atazanavir 300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a light meal in HIV-infected adult patients.

Figure 1: Mean (SD) Steady-State Plasma Concentrations of Atazanavir 400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-Infected Adult Patients



Absorption
Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200 to 800 mg once daily. Steady state is achieved between Days 4 and 8, with an accumulation of approximately 2.3 fold.

Food Effect
Administration of atazanavir with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400-mg dose of atazanavir with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in C_{max} relative to the fasting state. Administration of a single 400-mg dose of atazanavir with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration of atazanavir with either a light meal or high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately one-half compared to the fasting state.

Coadministration of a single 300-mg dose of atazanavir and a 100-mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2 to 5 hours. Coadministration of atazanavir with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state.

Distribution
Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients dosed with atazanavir 400 mg once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for atazanavir (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5) ranged between 0.11 and 4.42.

Metabolism
Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity. *In vitro* studies using human liver microsomes suggested that atazanavir is metabolized by CYP3A.

Elimination
Following a single 400 mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. The mean elimination half- life of atazanavir in healthy volunteers (n=214) and HIV-infected adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

Specific Populations
Renal Impairment
In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age-, weight-, and gender-matched subjects with normal renal function. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and Cmin were approximately 25% to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. Atazanavir is not recommended for use in HIV-treatment-experienced patients with end-stage renal disease managed with hemodialysis [*see Dosage and Administration (2.7)*].

Hepatic Impairment
Atazanavir has been studied in adult subjects with moderate-to-severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean $AUC_{(0-\infty)}$ was 42% greater in subjects with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy volunteers. A dose reduction to 300 mg is recommended for patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure as increased concentrations of atazanavir are expected. Atazanavir is not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of atazanavir in combination with ritonavir has not been studied in subjects with hepatic impairment; thus, coadministration of atazanavir with ritonavir is not recommended for use in patients with any degree of hepatic impairment [*see Dosage and Administration (2.8)*].

Pediatrics
The pharmacokinetic parameters for atazanavir at steady state in pediatric patients taking the capsule formulation were predicted by a population pharmacokinetic model and are summarized in Table 19 by weight ranges that correspond to the recommended doses [*see Dosage and Administration (2.4)*].

Table 19: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with Ritonavir in HIV-Infected Pediatric Patients

Body Weight (range in kg) [n]	atazanavir/ ritonavir Dose (mg)	C_{max} ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C_{min} ng/mL Geometric Mean (CV%)
15 to <35	200/100	3,303 (86%)	37,235 (84%)	538 (99%)
≥35	300/100	2,980 (82%)	37,643 (83%)	653 (89%)

Pregnancy
The pharmacokinetic data from HIV-infected pregnant women receiving atazanavir capsules with ritonavir are presented in Table 20.

Table 20: Steady-State Pharmacokinetics of Atazanavir with Ritonavir in HIV-Infected Pregnant Women in the Fed State

Pharmacokinetic Parameter	Atazanavir 300 mg with ritonavir 100 mg: 2nd Trimester (n=5[a])	3rd Trimester (n=20)	Postpartum[b] (n=34)
C_{max} ng/mL Geometric mean (CV%)	3,078.85 (50)	3,291.46 (48)	5,721.21 (31)
AUC ng•h/mL Geometric mean (CV%)	2,7657.1 (43)	34,251.5 (43)	61,990.4 (32)
C_{min} ng/mL[c] Geometric mean (CV%)	5,38.70 (46)	668.48 (50)	1,462.59 (45)

[a] Available data during the 2nd trimester are limited.
[b] Atazanavir peak concentrations and AUCs were found to be approximately 28% to 43% higher during the postpartum period (4 to 12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.
[c] C_{min} is concentration 24 hours post-dose.

Drug Interaction Data
Atazanavir is a metabolism-dependent CYP3A inhibitor, with a Kinact value of 0.05 to 0.06 min^{-1} and Ki value of 0.84 to 1 μM. Atazanavir is also a direct inhibitor for UGT1A1 (Ki=1.9 μM) and CYP2C8 (Ki=2.1 μM).

Atazanavir has been shown *in vivo* not to induce its own metabolism nor to increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for ritonavir for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir and dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. Atazanavir does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

Drug interaction studies were performed with atazanavir and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of atazanavir on the AUC, C_{max}, and C_{min} are summarized in Tables 21 and 22. Neither didanosine EC nor diltiazem had a significant effect on atazanavir exposures (see Table 22 for effect of atazanavir on didanosine EC or diltiazem exposures). Atazanavir did not have a significant effect on the exposures of didanosine (when administered as the buffered tablet), stavudine, or fluconazole. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 21: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/ Schedule	Atazanavir Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1: C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1-11 (n=19)	1 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
boceprevir	800 mg TID, d 1-6, 25-31	300 mg QD/ritonavir 100 mg QD, d 10-31	atazanavir: 0.75 (0.64-0.88) ritonavir: 0.73 (0.64-0.83)	atazanavir: 0.65 (0.55-0.78) ritonavir: 0.64 (0.58-0.72)	atazanavir: 0.51 (0.44-0.61) ritonavir: 0.55 (0.45-0.67)
clarithromycin	500 mg BID, d 7-10 (n=29) and d 18-21	400 mg QD, d 1-10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=31)	400 mg × 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=32)	400 mg × 1 dose 1 h after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
efavirenz	600 mg QD, d 7-20 (n=27)	400 mg QD, d 1-20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg QD, d 7-20 (n=13)	400 mg QD, d 1-6 (n=23) then 300 mg/ ritonavir 100 mg QD, 2 h before efavirenz, d 7-20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11-24 (pm) (n=14)	300 mg QD/ritonavir 100 mg QD, d 1-10 (pm) (n=22), then 400 mg QD/ritonavir 100 mg QD, d 11-24 (pm), (simultaneously with efavirenz) (n=14)	1.17 (1.08, 1.27)	1 (0.91, 1.10)	0.58 (0.49, 0.69)
famotidine	40 mg BID, d 7-12 (n=15)	400 mg QD, d 1-6 (n=45), d 7-12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40,0.87)	0.58 (0.37,0.89)
	40 mg BID, d 7-12 (n=14)	400 mg QD (pm), d 1-6 (n=14), d 7-12 (10 h after, 2 h before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID, d 11-20 (n=14)[c]	300 mg QD/ritonavir 100 mg QD, d 1-10 (n=46),d 11-20d (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75,0.89	0.72 (0.64, 0.81)
	20 mg BID, d 11-17 (n=18)	300 mg QD/ritonavir 100 mg QD/ tenofovir DF 300 mg QD, d 1-10 (am) (n=39), d 11-17 (am) (simultaneous administration with am famotidine) (n=18)[d,e]	0.91 (0.84, 0.99)	0.90 (0.82,0.98)	0.81 (0.64, 0.81)
famotidine	40 mg QD (pm), d 18 to 24 (n=20)	300 mg QD/ritonavir 100 mg QD/ tenofovir DF 300 mg QD, d 1 to 10 (am) (n=39), d 18-24 (am) (12 h after pm famotidine) (n=20)[e]	0.89 (0.81,0.97)	0.88 (0.80,0.96)	0.77 (0.63,0.93)
	40 mg BID, d 18 to 24 (n=18)	300 mg QD/ritonavir 100 mg QD/ tenofovir DF 300 mg QD, d 1 to 10 (am (n=39), d 18 to 24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18)e	0.74 (0.66,0.84)	0.79 (0.70,0.88)	0.72 (0.63,0.83)
	40 mg BID, d 11 to 20 (n=15)	300 mg QD/ritonavir 100 mg QD, d 1 to 10 (am) (n=46), then 400 mg QD/ritonavir 100 mg QD, d 11 to 20 (am) (n=15)	1.02 (0.87,1.18)	1.03 (0.86,1.22)	0.86 (0.68,1.08)
grazoprevir/ elbasvir	grazoprevir 200 mg QD d 1 to 35 (n = 11)	300 mg QD/ritonavir 100 mg QD	1.12 (1.01, 1.24)	1.43 (1.30, 1.57)	1.23 (1.13, 1.34)
	elbasvir 50 mg QD d 1 to 35 (n = 8)	300 mg QD/ritonavir 100 mg QD	1.02 (0.96, 1.08)	1.07 (0.98,1.17)	1.15 (1.02, 1.29)
ketoconazole	200 mg QD, d 7 to 13 (n=14)	400 mg QD, d 1 to 13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[f,g]	200 mg BID, d 1 to 23 (n=23)	300 mg QD/ritonavir 100 mg QD, d 4 to 13, then 400 mg QD/ ritonavir 100 mg QD, d 14 to 23 (n=23)[h]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg QD, d 7 to12 (n=16)[i]	400 mg QD, d 1 to 6 (n=48), d 7 to 12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11 to 20 (n=15)[i]	300 mg QD/ ritonavir 100 mg QD, d 1 to 20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17 to 23 (am) (n=13)	300 mg QD/ritonavir 100 mg QD, d 7 to 16 (pm) (n=27), d 17 to 23 (pm) (n=13)[j,k]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20 mg QD, d 17 to 23 (am) (n=14)	300 mg QD/ ritonavir 100 mg QD, d 7 to 16 (am) (n=27), then 400 mg QD/ritonavir 100 mg QD, d 17 to 23 (am) (n=14)[l,m]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.13 (0.96, 1.32)	1.06 (0.90, 1.26)	NA
rifabutin	150 mg QD, d 15 to 28 (n=7)	400 mg QD, d 1 to 28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
rifampin	600 mg QD, d 17 to 26 (n=16)	300 mg QD/ ritonavir 100 mg QD, d 7 to 16 (n=48), d 17 to 26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[n]	100 mg QD, d 11 to 20 (n=28)	300 mg QD, d 1-20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir DF[o]	300 mg QD, d 9 to 16 (n=34)	400 mg QD, d 2 to16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15 to 42 (n=10)	300 mg/ ritonavir 100 mg QD, d 1 to 42 (n=10)	0.72[p] (0.50, 1.05)	0.75[p] (0.58, 0.97)	0.77[p] (0.54, 1.10)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2 to 3, 22 to 30; 400 mg BID, d 1, 21 (n=20)	300 mg/ ritonavir 100 mg QD, d 11to 30 (n=20)	0.87 (0.80, 0.96)	0.88 (0.82, 0.95)	0.80 (0.72, 0.90)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2 to 3, 22 to 30; 100 mg BID, d 1, 21 (n=8)	300 mg/ ritonavir 100 mg QD, d 11 to 30 (n=8)	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

[a] Data provided are under fed conditions unless otherwise noted.
[b] All drugs were given under fasted conditions.
[c] Atazanavir 300 mg plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46-fold higher relative to atazanavir 400mg once daily alone.
[d] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir DF 300mg.
[e] Atazanavir /ritonavir/tenofovir DF was administered after a light meal.
[f] Study was conducted in HIV-infected individuals.
[g] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42,2.87), 2.28 (1.54, 3.38), and 1.80 (0.94,3.45), respectively, for atazanavir/ritonavir 400/100 mg.
[h] Parallel group design; n=23 for atazanavir/ritonavir plus nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.
[i] Omeprazole 40 mg was administered on an empty stomach 2 hours before atazanavir.
[j] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and atazanavir 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.
[k] Atazanavir 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1 to 6).
[l] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and atazanavir 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour after omeprazole. Effects on atazanavir concentrations were similar when atazanavir 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.
[m] Atazanavir 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in Cmax (26%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1 to 6).
[n] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.
[o] Note that similar results were observed in studies where administration of tenofovir DF and atazanavir was separated by 12 hours.
[p] Ratio of atazanavir plus ritonavir plus tenofovir DF to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote[n]). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir DF were: C_{max} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected individuals.
NA = not available.

Table 22: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir[a]

Coadministered Drug	Coadministered Drug Dose/ Schedule	Atazanavir Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1: C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1-20 (n=10)	300 mg QD/ ritonavir 100 mg QD, d 11-20 (n=10)	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg QD, d 7-11 (n=19) and d 19-23	400 mg QD, d 1-11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
boceprevir	800 mg TID, d 1-6, 25-31	300 mg QD/ ritonavir 100 mg QD, d 10-31	0.93 (0.80, 1.08)	0.95 (0.87, 1.05)	0.82 (0.68, 0.98)
clarithromycin	500 mg BID, d 7-10 (n=21) and d 18-21	400 mg QD, d 1-10 (n=21)	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60 (2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
ddI (enteric-coated [EC] capsules)[b]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2-8 (n=34)	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD/ ritonavir 100 mg QD, d 9-19 (n=31)	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
diltiazem	180 mg QD, d 7-11 (n=28) and d 19-23	400 mg QD, d 1-11 (n=28)	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2.14, 2.73) desacetyl-diltiazem: 2.21 (2.02, 2.42)
ethinyl estradiol & norethindrone[c]	Ortho-Novum® 7/7/7 QD, d 1-29 (n=19)	400 mg QD, d 16-29 (n=19)	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
ethinyl estradiol & norgestimate[d]	Ortho Tri-Cyclen® QD, d 1-28 (n=18), then Ortho Tri-Cyclen® LO QD, d 29-42e (n=14)	300 mg QD/ ritonavir 100 mg QD, d 29-42 (n=14)	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate:[f] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[f] 1.85 (1.67, 2.05	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[f] 2.02 (1.77, 2.31)
glecaprevir/ pibrentasvir	300 mg glecaprevir (n=12)	300 mg QD/ritonavir 100 mg QD (n=12)	≥4.06[g] (3.15, 5.23)	≥6.53[g] (5.24, 8.14)	≥14.3[g] (9.85, 20.7)
	300 mg glecaprevir (n=12)	300 mg QD/ritonavir 100 mg QD (n=12)	≥1.29[g] (1.15, 1.45)	≥1.64[g] (1.48, 1.82)	≥2.29[g] (1.95, 2.68)
grazoprevir/ elbasvir	grazoprevir 200 mg QD d 1 -35 (n = 12)	300 mg QD/ritonavir 100 mg QD d 1 - 35 (n=1)	6.24 (4.42, 8.81)	10.58 (7.78, 14.39)	11.64 (7.96, 17.02)
	elbasvir 50 mg QD d 1 -35 (n = 10)	300 mg QD/ritonavir 100 mg QD d 1 - 35 (n=10)	4.15 (3.46, 4.97)	4.76 (4.07, 5.56)	6.45 (5.51 7.54)
methadone	Stable maintenance dose, d 1-15 (n=16)	400 mg QD, d 2-15 (n=16)	(R)-methadone[h] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone[h] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadoneh 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[i,j]	200 mg BID, d 1-23 (n=23)	300 mg QD/ ritonavir 100 mg QD, d 4-13, then 400 mg QD/ ritonavir 100 mg QD, d 14-23 (n=23)	1.17 (1.09, 1.25) 1.21 (1.11, 1.32)	1.25 (1.17, 1.34) 1.26 (1.17, 1.36)	1.32 (1.22, 1.43) 1.35 (1.25, 1.47)
omeprazole[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1-12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1-10 then 150 mg QD, d 11-20 (n=3)	600 mg QD,[l] d 11-20 (n=3)	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190)
	150 mg twice weekly, d 1-15 (n=7)	300 mg QD/ ritonavir 100 mg QD, d 1-17 (n=7)	2.49[m] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48[m] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40[m] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.60 (1.39, 1.85)	1.31 (1.23, 1.39)	NA
rosiglitazone[m]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2-7, then 300 mg QD/ ritonavir 100 mg QD, d 8-17 (n=14)	1.08 (1.03, 1.13) 0.97 (0.91, 1.04)	1.35 (1.26, 1.44) 0.83 (0.77, 0.89)	NA NA
rosuvastatin	10 mg single dose	300 mg QD/ ritonavir 100 mg QD for 7 days	↑7-fold[o]	↑3-fold[o]	NA
Saquinavir[p] (soft gelatin capsules)	1200 mg QD, d 1-13 (n=7)	400 mg QD, d 7-13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
sofosbuvir/ velpatasvir/ voxilaprevir	400 mg sofosbuvir single dose (n=15)	300 mg/100 mg ritonavir single dose (n=15)	1.29 (1.09, 1.52) sofosbuvir metabolite GS-331007 1.05 (0.99, 1.12)	1.40 (1.25, 1.57) sofosbuvir metabolite GS-331007 1.25 (1.16, 1.36)	NA
	100 mg velpatasvir single dose (n=15)	300 mg/100 mg ritonavir single dose (n=15)	1.29 (1.07, 1.56)	1.93 (1.58, 2.36)	NA
	100 mg voxilaprevir single dose (n=15)	300 mg/100 mg ritonavir single dose (n=15)	4.42 (3.65, 5.35)	4.31 (3.76, 4.93)	NA
tenofovir DF[q]	300 mg QD, d 9-16 (n=33) and d 24-30 (n=33)	400 mg QD, d 2-16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1-7 (pm) (n=14) d 25-34 (pm) (n=12)	300 mg QD/ritonavir 100 mg QD, d 25-34 (am) (n=12)[r]	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2-3, 22-30; 400 mg BID, d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11-30 (n=20)	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID, d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11-30 (n=8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1-12 (n=19)	400 mg QD, d 7-12 (n=19)	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] Data provided are under fed conditions unless otherwise noted.
[b] 400 mg ddI EC and atazanavir were administered together with food on Days 8 and 19.
[c] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.
[d] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.
[e] All subjects were on a 28-day lead-in period; one full cycle of Ortho Tri-Cyclen®. Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.
[f] 17-deacetyl norgestimate is the active component of norgestimate.
[g] Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.
[h] (R)-methadone is the active isomer of methadone.
[i] Study was conducted in HIV-infected individuals.
[j] Subjects were treated with nevirapine prior to study entry.
[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after atazanavir on Day 7; and was given alone 2 hours after a light meal on Day 20.
[l] Not the recommended therapeutic dose of atazanavir.
[m] When compared to rifabutin 150 mg QD alone d1 to 10 (n=14). Total of rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[n] Rosiglitazone used as a probe substrate for CYP2C8.
[o] Mean ratio (with/without coadministered drug). ↑indicates an increase in rosuvastatin exposure.
[p] The combination of atazanavir and saquinavir 1,200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1,200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1,200 mg TID.
[q] Note that similar results were observed in a study where administration of tenofovir DF and atazanavir was separated by 12 hours.
[r] Administration of tenofovir DF and atazanavir was temporally separated by 12 hours.
NA = not available.

12.4 Microbiology
Mechanism of Action
Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). 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.

Antiviral Activity in Cell Culture
Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NNRTIs (delavirdine, efavirenz, and nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Resistance
In Cell Culture: HIV-1 isolates with a decreased susceptibility to ATV have been selected in cell culture and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates with 93- to 183-fold reduced susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to ATV resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies of Treatment-Naive Patients: Comparison of Ritonavir-Boosted atazanavir vs. Unboosted atazanavir: Study AI424-089 compared atazanavir 300 mg once daily with ritonavir 100 mg vs. Atazanavir 400 mg once daily when administered with lamivudine and extended-release stavudine in HIV-infected treatment-naive patients. A summary of the number of virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 23.

Table 23: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted atazanavir vs. Unboosted atazanavir: Randomized Patients

	Atazanavir 300 mg + Ritonavir 100 mg (n=95)	Atazanavir 400 mg (n=105)
Virologic Failure (≥50 copies/mL) at Week 96	15 (16%)	34 (32%)
Virologic Failure with Genotypes and Phenotypes Data	5	17
Virologic Failure Isolates with ATV-resistance at Week 96	0/5(0%)[b]	4/17 (24%)[b]
Virologic Failure Isolates with I50L Emergence at Week 96[c]	0/5(0%)[b]	2/17 (12%)[b]
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%)[b]	11/17 (65%)[b]

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.
[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.
[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Clinical Studies of Treatment-Naive Patients Receiving atazanavir 300 mg with Ritonavir 100 mg: In Phase III Study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Naive Patients Receiving atazanavir 400 mg without Ritonavir:
ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure on atazanavir 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of ATV therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive patients, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to ATV but retained in cell culture susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L substitution on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Experienced Patients: In studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir DF and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other substitutions that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance substitutions were present in the HIV-1 virus of the patient at baseline, ATV resistance developed through substitutions associated with resistance to other PIs and could include the development of the I50L substitution. The I50L substitution has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

Clinical Studies of Pediatric Subjects in AI424-397 (PRINCE I) and AI424-451 (PRINCE II):
Treatment-emergent ATV/RTV resistance-associated amino acid substitution M36I in the protease was detected in the virus of one subject among treatment failures in AI424-397. In addition, three known resistance-associated substitutions for other PIs arose in the viruses from one subject each (L19I/R, H69K/R, and I72I/V). Reduced susceptibility to ATV, RTV, or ATV/RTV was not seen with these viruses. In AI424-451, ATV/RTV resistance-associated substitutions G16E, V82A/I/T, I84V, and/or L90M arose in the viruses of two subjects. The virus population harboring the M46M/V, V82V/I, I84I/V, and L90L/M substitutions acquired phenotypic resistance to RTV (RTV phenotypic fold-change of 3.5, with a RTV cutoff of 2.5-fold change). However, these substitutions did not result in phenotypic resistance to ATV (ATV phenotypic fold-change of <1.8, with an ATV cutoff of 2.2-fold change). Secondary PI resistance-associated amino acid substitutions also arose in the viruses of one subject each, including V11V/I, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61E/G emerged in the viruses of two subjects who failed treatment with ATV/RTV. Viruses from nine subjects in the two studies developed NRTI resistance-associated substitutions: K65K/R (n=1), M184V (n=7), and T215I (n=1).

Cross-Resistance
Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced patients showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to ATV, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

Baseline Genotype/Phenotype and Virologic Outcome Analyses
Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy. An association between virologic response at 48 weeks and the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 24. Overall, both the number and type of baseline PI substitutions affected response rates in treatment-experienced patients. In the ATV/RTV group, patients had lower response rates when 3 or more baseline PI substitutions, including a substitution at position 36, 71, 77, 82, or 90, were present compared to patients with 1to 2 PI substitutions, including one of these substitutions.

Table 24: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Number and Type of Baseline PI Substitutions[a]	Virologic Response = HIV RNA ATV/RTV (n=110)	<400 copies/mL[b] LPV/RTV (n=113)
3 or more primary PI substitutions including[c]:		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)
I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
Number of baseline primary PI substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0-2 PI substitutions	75% (50/67)	75% (50/67)
3-4 PI substitutions	41% (14/34)	43% (12/28)
5 or more PI substitutions	0% (0/9)	28% (5/18)

[a] Primary substitutions include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.
[b] Results should be interpreted with caution because the subgroups were small.
[c] There were insufficient data (n<3) for PI substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 25). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for atazanavir.

Table 25: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	Virologic Response = HIV RNA ATV/RTV (n=111)	<400 copies/mL[b] LPV/RTV (n=111)
0-2	71% (55/78)	70% (56/80)
>2-5	53% (8/15)	44% (4/9)
>5-10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

[a] Fold change susceptibility in cell culture relative to the wild-type reference.
[b] Results should be interpreted with caution because the subgroups were small.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL (no observable adverse effect level) in females, (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir, non-pregnant patients). In the rat study, no drug-related increases in tumor incidence were observed at doses up to 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Mutagenesis
Atazanavir tested positive in an *in vitro* clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay).

Impairment of Fertility
At the systemic drug exposure levels (AUC) 0.9 (in male rats) or 2.3 (in female rats) times that of the human clinical dose, (300 mg/day atazanavir boosted with 100 mg/day ritonavir) significant effects on mating, fertility, or early embryonic development were not observed.

14 CLINICAL STUDIES
14.1 Adult Patients without Prior Antiretroviral Therapy
Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of atazanavir /ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofovir DF-emtricitabine in HIV-1 infected treatment-naive subjects. Study AI424-138 was a 96-week, open-label, randomized, multicenter study, comparing atazanavir (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir DF with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients had a mean age of 36 years (range: 19 to 72), 49% were Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm^3 (range: 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 log_{10} copies/mL (range: 2.60 to 5.88 log_{10} copies/mL). Treatment response and outcomes through Week 96 are presented in Table 26.

Table 26: Outcomes of Treatment Through Week 96 in Treatment-Naive Adults (Study AI424-138)

Outcome	Atazanavir 300 mg + ritonavir 100 mg (once daily) with tenofovir DF/ emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir DF /emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.
[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.
[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% (difference estimate: 1.7% [95% confidence interval: -3.8%, 7.1%]).
[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% (difference estimate: 6.1% [95% confidence interval: 0.3%, 12%]).
[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.
[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the atazanavir/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks, the median increase from baseline in CD4+ cell count was 261cells/mm^3 for the atazanavir /ritonavir arm and 273 cells/mm3 for the lopinavir/ritonavir arm.

Study AI424-034: Atazanavir once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study AI424-034 was a randomized, double-blind, multicenter trial comparing atazanavir (400 mg once daily) to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4+ cell count was 321 cells/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 log_{10} copies/mL (range: 2.2 to 5.9 log_{10} copies/mL). Treatment response and outcomes through Week 48 are presented in Table 27.

Table 27: Outcomes of Randomized Treatment Through Week 48 in Treatment-Naive Adults (Study AI424-034)

Outcome	Atazanavir 400 mg once daily + lamivudine + zidovudine[d] (n=405)	efavirenz 600 mg once daily + lamivudine + zidovudine[d] (n=405)
Responder[a]	67% (32%)	62% (37%)
Virologic failure[b]	20%	21%
Rebound	17%	16%
Never suppressed through Week 48	3%	5%
Death	-	<1%
Discontinued due to adverse event	5%	7%
Discontinued for other reasons[c]	8%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.
[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Through 48 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA≥100,000 copies/mL) was comparable for the atazanavir and efavirenz arms. The mean increase from baseline in CD4 + cell count was 176 cells/mm^3 for the atazanavir arm and 160 cells/mm^3 for the efavirenz arm.

Study AI424-008: Atazanavir 400 mg once daily compared to atazanavir 600 mg once daily, and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and lamivudine twice daily. Study AI424-008 was a 48-week, randomized, multicenter trial, blinded to dose of atazanavir, comparing atazanavir at two dose levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cell count was 295 cells/mm^3 (range: 4 to 1003 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.7 log_{10} copies/mL (range: 1.8 to 5.9 log_{10} copies/mL). Treatment response and outcomes through Week 48 are presented in Table 28.

Table 28: Outcomes of Randomized Treatment Through Week 48 in Treatment-Naive Adults (Study AI424-008)

Outcome	Atazanavir 400 mg once daily + lamivudine + stavudine (n=181)	nelfinavir 1,250 mg twice daily + lamivudine + stavudine (n=91)
Responder[a]	67% (33%)	59% (38%)
Virologic failure[b]	24%	27%
Rebound	14%	14%
Never suppressed through Week 48	10%	
Death	<1%	-
Discontinued due to adverse event	1%	3%
Discontinued for other reasons[c]	7%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 MonitorTM Assay, test version 1 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
c Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 234 cells/mm3 for the atazanavir 400-mg arm and 211 cells/mm3 for the nelfinavir arm.

14.2 Adult Patients with Prior Antiretroviral Therapy
Study AI424-045: Atazanavir once daily + ritonavir once daily compared to atazanavir once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir DF + one NRTI. Study AI424-045 was a randomized, multicenter trial comparing atazanavir (300 mg once daily) with ritonavir (100 mg once daily) to atazanavir (400 mg once daily) with saquinavir soft gelatin capsules (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg twice daily), each in combination with tenofovir DF and one NRTI, in 347 (of 358 randomized) patients who experienced virologic failure on HAART regimens containing PIs, NNRTIs, and NRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 85 weeks for NNRTIs, and 283 weeks for NRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline CD4+ cell count was 338 cells/mm^3 (range: 14 to 1543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/mL (range: 2.6 to 5.88 log_{10} copies/mL).

Treatment outcomes through Week 48 for the atazanavir /ritonavir and lopinavir/ritonavir treatment arms are presented in Table 29. Atazanavir/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that atazanavir/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of quantification [*see Microbiology, Tables 24 and 25 (12.4)*].

Table 29: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)

	Atazanavir 300 mg + ritonavir 100 mg once daily + tenofovir DF + 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily + tenofovir DF + 1 NRTI (n=118)	Differencea (Atazanavir lopinavir/ritonavir) (CT)
HIV RNA Change from	-1.58	-1.70	+0.12[c]
Baseline (log_{10} copies/mL)b	116	123	(-0.17, 0.41)
CD4+ Change from			-7
Baseline (cells/mm^3)d			(-67, 52)
Percent of Patients			
Responding[e]			-2.2%
HIV RNA <400 copies/mL[b]	55%	57%	(-14.8%, 10.5%)
HIV RNA <50 copies/mL[b]	38%	45%	-7.1%
			(-19.6%, 5.4%)

[a] Time-averaged difference through Week 48 for HIV RNA; Week 48 difference in HIV RNA percentages and CD4+ mean changes, atazanavir/ritonavir vs lopinavir/ritonavir; CI = 97.5% confidence interval for change in HIV RNA; 95% confidence interval otherwise.
[b] Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.
[c] Protocol-defined primary efficacy outcome measure.
[d] Based on patients with baseline and Week 48 CD4+ cell count measurements (atazanavir/ritonavir, n=85; lopinavir/ritonavir, n=93).
[e] Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48.

No patients in the atazanavir/ritonavir treatment arm and three patients in the lopinavir/ritonavir treatment arm experienced a new-onset CDC Category C event during the study.

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for atazanavir 400 mg with saquinavir (n=115) was -1.55 log_{10} copies/mL, and the time-averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm^3. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of atazanavir and saquinavir did not provide adequate efficacy *[see Drug Interactions (7)]*.

Study AI424-045 also compared changes from baseline in lipid values. *[See Adverse Reactions (6.1).]*

Study AI424-043: Study AI424-043 was a randomized, open-label, multicenter trial comparing Atazanavir (400 mg once daily) to lopinavir/ritonavir (400/100 mg twice daily), each in combination with two NRTIs, in 300 patients who experienced virologic failure to only one prior PI-containing regimen. Through 48 weeks, the proportion of patients with plasma HIV-1 RNA <400 (<50) copies/mL was 49% (35%) for patients randomized to atazanavir (n=144) and 69% (53%) for patients randomized to lopinavir/ritonavir (n=146). The mean change from baseline was -1.59 log_{10} copies/mL in the atazanavir treatment arm and -2.02 log_{10} copies/mL in the lopinavir/ritonavir arm. Based on the results of this study, atazanavir without ritonavir was inferior to lopinavir/ritonavir in PI-experienced patients with prior virologic failure and is not recommended for such patients.

14.3 Pediatric Patients
Pediatric Trials with atazanavir capsules
Assessment of the pharmacokinetics, safety, tolerability, and virologic response of atazanavir capsules was based on data from the open-label, multicenter clinical trial PACTG 1020A which included patients from 6 years to 21 years of age. In this study, 105 patients (43 antiretroviralnaive and 62 antiretroviral-experienced) received once daily atazanavir capsule formulation, with or without ritonavir, in combination with two NRTIs.

One-hundred five (105) patients (6 to less than 18 years of age) treated with the atazanavir capsule formulation, with or without ritonavir, were evaluated. Using an ITT analysis, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm^3 in antiretroviral-naive patients and 220 cells/mm^3 in antiretroviral-experienced patients.

16 HOW SUPPLIED/STORAGE AND HANDLING
Atazanavir capsules, 150 mg are off-white to pale yellow colored granular powder filled in size "1" hard gelatin capsules with green opaque cap imprinted with "H" in black color and light green opaque body imprinted with "A6" in black color. They are supplied as follows:

Bottle of 60 capsules
Bottle of 1000 capsules
Carton of 100 (10x10s) unit-dose capsules

Atazanavir capsules, 200 mg are off-white to pale yellow colored granular powder filled in size "0" hard gelatin capsules with green opaque cap imprinted with "H" in black color and light green opaque body imprinted with "A7" in black color. They are supplied as follows

Bottle of 60 capsules
Bottle of 1000 capsules
Carton of 100 (10x10s) unit-dose capsules

Atazanavir capsules, 300 mg are off-white to pale yellow colored granular powder filled in size "00" hard gelatin capsules with orange opaque cap imprinted with "H" in black color and green opaque body imprinted with "A8" in black color. They are supplied as follows
Bottle of 30 capsules
Bottle of 500 capsules
Carton of 100 (10x10s) unit-dose capsules

STORAGE CONDITION: Store at temperatures not exceeding 30°C. Protect from moisture.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling *(Patient Information and Instructions for Use)*.

Atazanavir capsules are not a cure for HIV infection. Advise patients to remain under the care of a healthcare provider while using atazanavir capsules.

Cardiac Conduction Abnormalities
Inform patients that atazanavir capsules may produce changes in the electrocardiogram (eg, PR prolongation). Tell patients to consult their healthcare provider if they are experiencing symptoms such as dizziness or light headedness *[see Warnings and Precautions (5.1)]*.

Severe Skin Reaction
Inform patients that there have been reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with atazanavir capsules use. Advise patients that if signs or symptoms of severe skin reactions or hypersensitivity reactions develop, they must discontinue atazanavir capsules and seek medical evaluation immediately *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Hyperbilirubinemia
Inform patients that asymptomatic elevations in indirect bilirubin have occurred in patients receiving atazanavir capsules. This may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if the patient has cosmetic concerns *[see Warnings and Precautions (5.8)]*.

Chronic Kidney Disease
Inform patients that treatment with atazanavir capsules may lead to the development of chronic kidney disease, and to maintain adequate hydration while taking atazanavir capsules [*see Warnings and Precautions (5.5)*].

Nephrolithiasis and Cholelithiasis
Inform patients that kidney stones and/or gallstones have been reported with atazanavir capsules use. Some patients with kidney stones and/or gallstones required hospitalization for additional management and some had complications. Discontinuation of atazanavir capsules may be necessary as part of the medical management of these adverse events *[see Warnings and Precautions (5.6)]*.

Drug Interactions
Atazanavir capsules may lead to significant interaction with some drugs; therefore, advise patients to report the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort, to their healthcare provider prior to use *[see Contraindications (4), Warnings and Precautions (5.7)]*.

Immune Reconstitution Syndrome
Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.10)]*.

Fat Redistribution
Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.11)]*.

Dosing Instructions
Advise patients to take atazanavir capsules with food every day and take other concomitant antiretroviral therapy as prescribed. Atazanavir capsules must always be used in combination with other antiretroviral drugs. Advise patients that they should not alter the dose or discontinue therapy without consulting with their healthcare provider. Tell patients if a dose of atazanavir capsules is missed, they should take the dose as soon as possible and then return to their normal schedule; however, if a dose is skipped the patient should not double the next dose.

Pregnancy
Inform pregnant patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atazanavir capsules during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry *[see Use in Specific Populations (8.1)]*.

Lactation
Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk. Atazanavir capsules can also be passed to the baby in breast milk and it is not known whether it could harm the baby *[see Use in Specific Populations (8.2)]*.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT: For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Licensed Product is manufactured under a license from the 'Medicines Patent Pool'.

Manufactured by:
HETERO **HETERO LABS LIMITED**
Unit-III, Formulation
Plot No. 22-110, I.D.A.,
Jeedimetla, Hyderabad 500 055,
Telangana, INDIA

Imported and Distributed by:
CAMBER PHARMACEUTICALS, INC.
Unit 503-A ITC Bldg., 337 Sen. Gil Puyat
Avenue, Bel-Air, Makati City, Philippines.

Registration No.
150mg - DR-XY48192
200mg - DR-XY48191
300mg - DR-XY48190

Date of First Authorization : July 2022

Date of Revision of Package Insert : October 2023

2055783

11152