

		AZANAVIR R 150/200/30	0
HIGHLIGHTS OF PRESCRI These highlights do not	150 mg, 20 F Bing information	00 mg and 300 mg Capsul Protease Inhibitor	
effectively. See full pres ATAZANAVIR capsules, fo Initial U.S. Approval: 200	cribing information for A7 r oral use	TAZANAVIR CAPSULES.	THE STATE OF THE S
Opaque cap imprinted with	n "H" in black color and Lig	ht Green opaque Body im	hard gelatin capsules with printed with "A6" in black o hard gelatin capsules with
Opaque cap imprinted with Atazanavir 300mg Off whi orange Opaque cap imprint	n "H" in black color and Lig te to pale yellow colored g ted with "H" in black color a	ht Green opaque Body im ranular powder filled in si and Green opaque Body im	printed with "A7" in black o ze 00 hard gelatin capsule printed with "A8" in black o
Dosage and Administration Testing Prior to Initia with atazanavir capsi	ition and During Treatment ules (2.2)		10/2017
Dosage of Atazanavir Caps Contraindications (4) Warnings and Precautions Chronic Kidney Disease (5)	ules in Pediatric Patients (2 .5)	2.4)	05/2017 03/2018 10/2017
Atazanavir capsules are a the treatment of HIV-1 infe	protease inhibitor indicated ction for patients 6 years a	l for use in combination w nd older weighing at least	rith other antiretroviral ager 15 kg. (1)
 Pretreatment testing atazanavir capsules performed in patient 	g: Renal laboratory testing and continued during treat	g should be performed in tment with atazanavir cap ease prior to initiation of al	n all patients prior to initiat sules. Hepatic testing sho azanavir capsules and con
 atazanavir 400 mg or Treatment-experience (2.3) 	nce daily with food. (2.3) need adults: Atazanavir caps	ules 300 mg with ritona	00 mg once daily with fo
 be taken with food. (Pregnancy: Atazanavi for some concomitar 	2.4) ir capsules 300 mg with rito nt medications. (2.6)	navir 100 mg once daily wi	to exceed the adult dose and th food, with dosing modific 2.4, 2.6), renal impairment
and hepatic impairm Capsules: 150 mg, 200	ent (2.8). DOSAGE FORM mg, 300 mg. (3, 16)	MS AND STRENGTHS	
 Atazanavir capsules 	are contraindicated in pat	ients with previously der	monstrated hypersensitivit ons) to any of the compone
FULL PRESCRIBING INFO			
2 DOSAGE AND ADMII 2.1 Overview 2.2 Testing Prior to	NISTRATION Initiation and During Trea		sules
2.4 Dosage of Ataz 2.6 Dosage Adjust 2.7 Dosage in Pati	canavir Capsules in Adult Pa canavir Capsules in Pediatri ments in Pregnant Patients ents with Renal Impairment ments in Patients with Hen-	c Patients t	
3 DOSAGE FORMS AN 4 CONTRAINDICATION 5 WARNINGS AND PR	IS Ecautions	auc impairment	
	ction Abnormalities eactions		
5.6 Nephrolithiasis	and Cholelithiasis s Adverse Reactions Due to emia	Drug Interactions	
5.10 Immune Recor 5.11 Fat Redistribut 5.12 Hemophilia	nstitution Syndrome ion		
5.13 Resistance/Crc ADVERSE REACTION 6.1 Clinical Trial Ex 6.2 Postmarketing	IS xperience		
FULL PRESCRIBING INFO	RMATION		
	ISAGE dicated in combination wi rs and older weighing at lea		ents for the treatment of H
 Atazanavir capsules i risk of kernicterus. Use of atazanavir /rit 		nced patients should be gu	w the age of 3 months due ided by the number of base
2 DOSAGE AND ADMII 2.1 Overview • Atazanavir capsules	NISTRATION must be taken with food.	лі <i>в [зее іністоліо</i> юду (т.г.	- 7/].
the use of other coad inhibitors, dose sepa	sules. ral dosage of atazanavir ca Iministered drugs. When co ıration may be required <i>[se</i>	administered with H2-rece	ptor antagonists or proton-
patients with prior vi	without ritonavir are not re rologic failure [see Clinical of atazanavir capsules with	Studies (14)].	
profile of atazanavir should consult the	aily have not been establisl (cardiac effects, hyperbiliru complete prescribing infor ation and During Treatmer	binemia) and, therefore, is mation for ritonavir when	not recommended. Preso using ritonavir.
Renal laboratory testing sh during treatment with ataz creatinine clearance, and u	ould be performed in all pat zanavir capsules. Renal lab rinalysis with microscopic	tients prior to initiation of a oratory testing should in examination [<i>see Warning</i>	atazanavir capsules and con clude serum creatinine, esti s and Precautions (5.5, 5.6
atazanavir capsules and c (5.4)].	should be performed in pontinued during treatment ir Capsules in Adult Patien	with atazanavir capsules	
Table 1 displays the recomadults. Table 1 also display with other antiretroviral dr	mended dosage of atazana ys recommended dosage of ugs and H2-receptor antag	vir capsules in treatment- f atazanavir capsules and ri jonists (H2RA). Ritonavir i	naive and treatment-experi itonavir when given concom s required with several ataz bout the safe and effectiv
of ritonavir). The use of recommended.	atazanavir capsules in treat d Atazanavir Capsules and	ment-experienced adult pa Ritonavir Dosage in Adu	itients without ritonavir is n Its ^a
Treatment-N	aive Adult Patients	navir Capsules Once Ri Daily Dosage	Dosage 100 mg
in combination	erate ritonavir on with efavirenz xperienced Adult Patients	400 mg 400 mg 300 mg	N/A 100 mg 100 mg
in combination and tenofovir	on with both H2RA DF	400 mg	100 mg -reducing medications (eg,
or proton pump inhibitors 2.4 Dosage of Atazanav The recommended daily de	[PPIs]), and other antiretr ir Capsules in Pediatric Pa osage of atazanavir capsule	roviral drugs (eg, efaviren a tients es and ritonavir in pediatri	z, tenofovir DF, and didance c patients (6 years of age t
/	sed on body weight (see Ta d Dosage of Atazanavir Ca e) ^{a,b}	,	Pediatric Patients (6 to les
	Treatment-Experienced ^c	Atazanavir Capsules Da Dosage	Dosage
Less than 15 kg At least 15 kg to less to At least 35 kg Treatment-Naive, at le	han 35 kg east 13 years old and cann	Capsules not recommen 200 mg 300 mg not tolerate ritonavir ^c	ded N/A 100 mg 100 mg
At least 40 kg	, ,	400 mg	N/A
The same recommend	apsules and ritonavir simulations regarding the timing	and maximum doses of	concomitant PPIs and H2F
The same recommend adults also apply to per of acid-reducing medic and didanosine).	ations regarding the timing diatric patients. See <i>Drug Ir</i>	g and maximum doses of nteractions (7) for instructi , and other antiretroviral d	ons concerning coadminis rugs (eg, efavirenz, tenofo
The same recommend adults also apply to per of acid-reducing medic and didanosine). In treatment-experience When transitioning betweer formulation Cosage Adjustment: Table 4 includes the recommendation.	ations regarding the timing liatric patients. See <i>Drug Ir</i> ations (eg, H2RA or PPIs), ed patients, atazanavir caps of formulations, a change in or sin Pregnant Patients mended dosage of atazanar	g and maximum doses of interactions (7) for instruct, and other antiretroviral d sules must be administered dose may be needed. Consi-	ons concerning coadminisi irugs (eg, efavirenz, tenofo d with ritonavir. ult the dosing table for the s in treatment-naive and trea!
halfillisted adadatation of the same recommend adults also apply to per of acid-reducing medic and didanosine). In treatment-experience When transitioning between formulation 2.6 Dosage Adjustments Table 4 includes the recome experienced pregnant patic are no dosage adjustments in adults) [see Use in Specific Adams of the Comment of t	ations regarding the timing idarric patients. See <i>Drug Ir</i> ations (eg, H2RA or PPIs), ed patients, atazanavir caps in formulations, a change in os in Pregnant Patients mended dosage of atazana rests. In these natients, atazs.	a and maximum doses of theractions (7) for instruct, and other antiretroviral dose sules must be administered dose may be needed. Consi- vir capsules and ritonavir anavir capsules must be a ee Table 1 for the recomme	ons concerning coadminisirugs (eg, efavirenz, tenofo d with ritonavir. ult the dosing table for the s in treatment-naive and treat ddministered with ritonavir. ended atazanavir capsules o
hamiliniste adzalativi of The same recommend adults also apply to per of acid-reducing medic and didanosine). In treatment-experience when transitioning betweer formulation 2.6 Dosage Adjustment Table 4 includes the recomexperienced pregnant patie are no dosage adjustments in adults) [see Use in Spec Table 4: Recommended	ations regarding the timing liatric patients. See <i>Drug Ir</i> ations (eg, HZRA or PPIs), ed patients, atazanavir caps of formulations, a change in or sin Pregnant Patients mended dosage of atazanarents. In these patients, ataz for postpartum patients (sific Populations (8.1)]. It Dosage of Atazanavir Ca	a and maximum doses of thereactions (7) for instruct, and other antiretroviral doubles must be administered dose may be needed. Considered vir capsules and ritonavir anavir capsules must be a ee Table 1 for the recommen psules and Ritonavir in P	ons concerning coadminisirugs (eg, efavirenz, tenofo d with ritonavir. ult the dosing table for the s in treatment-naive and treat ddministered with ritonavir. ended atazanavir capsules coregnant Patients ^a
hamiliniste adzaliavir commenda dults also apply to per of acid-reducing medic and didanosine). In treatment-experience When transitioning betweer formulation 2.6 Dosage Adjustments Table 4 includes the recome experienced pregnant patis are no dosage adjustments in adults) [see Use in Spec Table 4: Recommended Regimulation Recommended R	ations regarding the timing liatric patients. See <i>Drug Ir</i> ations (eg, HZPA or PPIs), ed patients, atazanavir caps of formulations, a change in or sin Pregnant Patients mended dosage of atazanarents. In these patients, ataz for postpartum patients (sife <i>Populations (8.1)</i>], d Dosage of Atazanavir Ca	a and maximum doses of iteractions (7) for instructi, and other antiretroviral disules must be administered dose may be needed. Consilvir capsules and ritonavir in anavir capsules must be a see Table 1 for the recomme psules and Ritonavir in P Atazanavir Capsules Of Daily Dosage 300 mg	ons concerning coadministrugs (eg, efavirenz, tenofo d with ritonavir. ult the dosing table for the s in treatment-naive and treat diministered with ritonavir. ended atazanavir capsules or regnant Patients nce Ritonavir Once Daily Dosage
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hamble to the commendation of the commendation	ations regarding the timing liatric patients. See Drug Ir ations (eg, H2RA or PPIs), ed patients, atazanavir caps of formulations, a change in of sin Pregnant Patients mended dosage of atazanants. In these patients, atazanarits in these patients, atazanarits in these patients, atazanarits. In these patients, atazanarits and Dosage of Atazanavir Calling Propulations (8.1)]. d Dosage of Atazanavir Calling the Second or The there is the propulations (eg, efavire) and the H2RA or 17) for instructions concerning the trecommended for treatazanavir capsules with bot with Renal Impairment pairment, including those ustment is required for atazanavir at the mendialysis should retor recommended in HIV-tres is see Use in Specific Popus is in Patients with Hepatic Imended atazanavir capsule	a and maximum doses of interactions (7) for instruct, and other antiretroviral deules must be administered dose may be needed. Considered and interactions and	ons concerning coadministrugs (eg, efavirenz, tenofo d with ritonavir. ult the dosing table for the s in treatment-naive and treat dministered with ritonavir. anded atazanavir capsules of the company o
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Treatment-Naive and Treatment-Naive and Treatment-Experience or Tendovir DF Treatment-Naive and Treatment-Experience or Tendovir DF Treatment-Naive and Recommended Regimum Treatmented Pregnant patis are no dosage adjustments in adults) [see Use in Spec Table 4: Recommended Regimum Treatment-Experience or Tendovir DF Treatment-Experience or Tendovir DF In combination with eit tendovir DF See Drug Interactions (or PPIs), and other ant Atazanavir capsules are third trimester taking a 2.7 Dosage in Patients with renal im hemodialysis, no dose adjrenal disease managed wi Atazanavir capsules are managed with hemodialysis. The use of atazanavir capsules are managed with hemodialysis to dose adjrenal disease managed with tendoministeric managed with hemodialysis. The coadministration of an ot recommended. Table 5: Recommended Mild hepatic impairmer Moderate hepatic impairm Severe hepatic impairm Severe hepatic impairm Capsules are to 150 mg capsule with of Green opaque Cap improcolor. 200 mg capsule with of Green opaque Cap improcolor. 200 mg capsule with of Green opaque Cap improcolor. 4 CONTRAINDICATIONS Atazanavir capsules are continued on the coadministered or page opaque Cap improcolor. 4 CONTRAINDICATIONS Atazanavir capsules are continued on the coadministered or page opaque Cap improcolor. 4 CONTRAINDICATIONS Atazanavir capsule with of Green opaque Cap improcolor. 5 CONTRAINDICATIONS Atazanavir capsules are continued or c	ations regarding the timing litatric patients. See Drug Ir ations (eg, H2RA or PPIs), and patients, atazanavir caps of formulations, a change in or sin Pregnant Patients mended dosage of atazanants. In these patients, atazanavirs are proposed for postpartum patients (siffic Populations (8.1)]. If the Dosage of Atazanavir Ca the Drug of Caps of Atazanavir Ca the H2RA or the H2	and maximum doses of interactions (7) for instruction, and other antiretroviral discussion and interactions (7) for instruction and interaction and interactio	ons concerning coadminist rugs (eg, efavirenz, tenofor d with ritonavir. ult the dosing table for the sin treatment-naive and treat diministered with ritonavir. ended atazanavir capsules d regnant Patients and the regnant and the reg
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Treatment-Experience Treatment-Raive and other and othe	ations regarding the timing liatric patients. See Drug Ir actions (eg, H2RA or PPIs), and patients, atazanavir caps of formulations, a change in or sin Pregnant Patients mended dosage of atazanants. In these patients, atazanavir caps of for postpartum patients (siffic Populations (8:1)]. It dosage of Atazanavir Ca description of the H2RA or a description of the	and maximum doses of interactions (7) for instructions (7) for instruction (7) for instructions (7) for instructio	ons concerning coadminist rugs (eg, efavirenz, tenofor d with ritonavir. ult the dosing table for the sin treatment-naive and treat diministered with ritonavir. ended atazanavir capsules d regnant Patients* Toe Ritonavir Once Daily Dosage 100 mg Ince Ritonavir Once Daily Dosage Ince Ritonavir Once Daily Dosage Ince Patic Impair Ince Adults with Hepatic Impair Ince Once Daily Dosage Ince Daily Dosage Ince Daily Dosage In size 0 hard gelatin capsule Body imprinted with "A6" in a size 0 hard gelatin capsule Body imprinted with "A6" in a size 0 hard gelatin capsule Body imprinted with "A8" in a size 0 hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A8" in the size of hard gelatin capsule Body imprinted with "A9" in the size of hard gelatin capsule Body imprinted with "A9" in the size of hard gelatin capsule Body imprinted with "A9" in the size of hard gelatin capsule Body imprinted with "A9" in the size of hard gelatin capsule Body imprinted with "A
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1	
ANAVIR 50/200/300	 Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lurasidone (if atazanavir capsules are coadministered with ritonavir), lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John's wort, nevirapine, elbasvir/grazoprevir, glecaprevir/pibrentasvir, and sildenafil when
and 300 mg Capsule se Inhibitor	dosed as REVATIO®. (4)WARNINGS AND PRECAUTIONS
eeded to use ATAZANAVIR CAPSULES safely and	 Cardiac conduction abnormalities: PR interval prolongation may occur in some patients. ECG monitoring should be considered in patients with preexisting conduction system disease or when administered with
AVIR CAPSULES.	other drugs that may prolong the PR interval. (5.1, 7.3, 12.2, 17) Severe Skin Reactions: Discontinue if severe rash develops. (5.2, 17) Hyperbilirubinemia: Most patients experience asymptomatic increases in indirect bilirubin, which is
	reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.8)
owder filled in size 1 hard gelatin capsules with Green en opaque Body imprinted with "A6" in black colour.	 Hepatotoxicity: Patients with hepatitis B or C infection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment (2.8, 5.4, 8.8) Chronic kidney disease has been reported during postmarketing surveillance in HIV-infected patients treated
owder filled in size 0 hard gelatin capsules with Green en opaque Body imprinted with "A7" in black colour. r powder filled in size 00 hard gelatin capsules with	with atazanavir, with or without ritonavir. Consider alternatives in patients at high risk for renal disease or with preexisting renal disease. Monitor renal laboratory tests prior to therapy and during treatment.
een opaque Body imprinted with "A8" in black colour.	Consider discontinuation of atazanavir in patients with progressive renal disease. (5.5) • Nephrolithiasis and cholelithiasis have been reported. Consider temporary interruption or discontinuation.
	 (5.6) The concomitant use of atazanavir/ritonavir and certain other medications may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for
10/2017 05/2017 03/2018	potential drug interactions. (5.7, 7.3) • Patients receiving atazanavir may develop new onset or exacerbations of diabetes mellitus/hyperglycemia
10/2017	 (5.9), immune reconstitution syndrome (5.10), and redistribution/accumulation of body fat (5.11). Hemophilia: Spontaneous bleeding may occur and additional factor VIII may be required. (5.12)
D USAGEse in combination with other antiretroviral agents for	——————————————————————————————————————
er weighing at least 15 kg. (1) NISTRATION	To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Ild be performed in all patients prior to initiation of with atazanavir capsules. Hepatic testing should be ior to initiation of atazanavir capsules and continued	
ng with ritonavir 100 mg once daily with food or	of atazanavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)
00 mg with ritonavir 100 mg once daily with food.	 Pregnancy: Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. (8.1)
on body weight not to exceed the adult dose and must 00 mg once daily with food, with dosing modifications	 Lactation: Breastfeeding is not recommended. (8.2) Hepatitis B or C co-infection: Monitor liver enzymes. (5.4, 6.1) Renal impairment: Atazanavir is not recommended for use in treatment-experienced patients with end-
tant therapy (2.3, 2.4, 2.6), renal impairment (2.7),	stage renal disease managed with hemodialysis. (2.7, 8.7) • Hepatic impairment: Atazanavir is not recommended in patients with severe hepatic impairment.
D STRENGTHS	Atazanavir/ritonavir is not recommended in patients with any degree of hepatic impairment. (2.8, 8.8) See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
ATIONS	Revised: 06/2018
with previously demonstrated hypersensitivity (eg, or toxic skin eruptions) to any of the components of	
	7 DRUG INTERACTIONS 7.1 Potential for Atazanavir to Affect Other Drugs 7.2 Potential For Other Drugs To Affect Atazanavir
with Atazanavir Capsules	7.2 Potential For Other Drugs To Affect Atazanavir 7.3 Established and Other Potentially Significant Drug Interactions 7.4 Drugs With No Observed Interactions With Atazanavir
ents	8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy
	8.2 Lactation 8.4 Pediatric Use
pairment	8.5 Geriatric Use 8.6 Age/Gender 8.7 Impaired Renal Function
	8.8 Impaired Hepatic Function 10 OVERDOSAGE
	11 DESCRIPTION 12 CLINICAL PHARMACOLOGY
	12.1 Mechanism of Action 12.2 Pharmacodynamics
Interactions	12.3 Pharmacokinetics 12.4 Microbiology 13 NONCLINICAL TOXICOLOGY
	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 14 CLINICAL STUDIES
	14.1 Adult Patients without Prior Antiretroviral Therapy 14.2 Adult Patients with Prior Antiretroviral Therapy
	14.3 Pediatric Patients 16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION
	* Sections or subsections omitted from the full prescribing information are not listed.
	had complications. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, temporary interruption or
er antiretroviral agents for the treatment of HIV-1	discontinuation of therapy may be considered [see Adverse Reactions (6.2)]. 5.7 Risk of Serious Adverse Reactions Due to Drug Interactions
diatric patients below the age of 3 months due to the	Initiation of atazanavir with ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving atazanavir with ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or
atients should be guided by the number of baseline	induce CYP3A may increase or decrease concentrations of atazanavir with ritonavir, respectively. These interactions may lead to:
ee Microbiology (12.4)].	 clinically significant adverse reactions potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications. clinically significant adverse reactions from greater exposures of atazanavir with ritonavir.
	 loss of therapeutic effect of atazanavir with ritonavir and possible development of resistance.
depends on the treatment history of the patient and istered with H2-receptor antagonists or proton-pump	See Table 16 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations [see Drug Interactions (77)]. Consider the potential for drug interactions prior to and during atazanavir/irlonavir therapy; review concomitant medications during atazanavir/irlonavir threapy; and monitor for the adverse reactions associated with the concomitant medications [see Contraindications (4) and Drug
age and Administration (2.3, 2.4, and 2.6) and Drug ended for treatment-experienced adult or pediatric	Interactions (7)]. 5 8 Hyperhiliruhinemia
es (14)]. avir when ritonavir is administered in doses greater	Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative
he use of higher ritonavir doses may alter the safety ia) and, therefore, is not recommended. Prescribers	etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to atazanavir may be considered if
n for ritonavir when using ritonavir. Atazanavir Capsules	jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established [see Adverse Reactions (6.1]].
prior to initiation of atazanavir capsules and continued y testing should include serum creatinine, estimated nation [see Warnings and Precautions (5.5, 5.6)].	5 Q Diahatas Mallitus/Hynarolycamia
s with underlying liver disease prior to initiation of atazanavir capsules [see Warnings and Precautions	New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy,
	hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical

Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration

of triazolam or orally administered midazolam with

atazanavir may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory

Potential for serious and/or life-threatening events

peripheral vasospasm and ischemia of the extremities

such as acute ergot toxicity characterized by

Potential for serious and/or life-threatening

May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma

May increase the risk of ALT elevations due to

Coadministration of St. John's wort and atazanavir may result in loss of therapeutic effect and

Potential for serious reactions such as myopathy,

Both atazanavir and indinavir are associated with

Nevirapine substantially decreases atazanavir

exposure which may result in loss of therapeutic effect and development of resistance. Potential

isk for nevirapine-associated adverse reactions

due to increased nevirapine exposures.

an increase in glecaprevir and pibrentasy

reactions such as cardiac arrhythmias.

ınd other tissues.

concentrations.

development of resistance.

including rhabdomyolysis. Sildenafil^b when dosed as Potential for sildenafil-associated adverse events REVATIO® for the treatment (which include visual disturbances, hypotension, priapism, and syncope). hypertension

Ergot Derivatives

GI Motility Agent

Herbal Products

PDE5 Inhibitor

Reverse Transcriptase Inhibitors

Protease Inhibitors

WARNINGS AND PRECAUTIONS
 Cardiac Conduction Abnormalitie

Colour: 1 (Black)

HMG-CoA Reductase

Cisapride

Lovastatin, simvastatin

1 See Drug Interactions, Table 16 (7) for parenterally administered midazolam. 2 See Drug Interactions, Table 16 (7) for sildenafil when dosed as VIAGRA® for erectile dysfunction.

5.1 Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities [see Adverse Reactions (6.2) and Overdosage (10)]. In clinical trials that include electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of helinavir-treated patients (n=920), 5.2% of electrocardiogram reasymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with bad on-study electrocardiogram reasurements. Because of limited clinical experience in patients with patients with one of the patients with such as the patients of the patients with such as the patie

5.2 Severe Skin Reactions
In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with atazanavir. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of > 2%) are presented for the individual clinical

adverse reactions of moderate or severe rash (occurring at a rate or $\geq 2\%$) are presented for the individual clinical studies [see Adverse Reactions (6.1)]. Dosing with atazanavir was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions, including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome, have been reported in patients receiving atazanavir [see Contraindications (4) and Adverse Reactions (6.1)]. Atazanavir should be discontinued if severe rash develops.

5.4 Hepatotoxicity
Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment

may be at increased risk for developing further transaminase elevations in haptic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with atazanavir and during treatment [see Dosage and Administration (2.2), Adverse Reactions (6.1), and Use in Specific Populations (8.8)].

| 5.5 Chronic Kidney Disease | Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported |

during postmarketing surveillance. Reports included biopsy-proven cases of granulomatous interstitial nephritis associated with the deposition of atazanavir drug crystals in the renal parenchyma. Consider alternatives to atazanavir in patients at high risk for renal disease or with preexisting renal disease. Renal laboratory testing (including serum creatinine, estimated creatinine clearance, and urinalysis with microscopic examination) should be conducted in all patients prior to initiating therapy with atazanavir and continued during treatment with atazanavir. Expert consultation is advised for patients who have confirmed renal laboratory abnormalities while taking atazanavir. In patients with progressive kidney disease, discontinuation of atazanavir may be considered [see Dosage and Administration (2.2 and 2.7) and Adverse Reactions (6.2)].

5.6 Nephrolithiasis and Cholelithiasis
Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving atazanavir therapy. Some patients required hospitalization for additional management and some

Nevirapine

Hepatitis C Direct-Acting Elbasvir/grazoprevir Antivirals

In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established [see Adverse Reactions (6.2)]. 5.10 Immune Reconstitution Syndrome itution syndrome has been reported in patients treated with combination antiretroviral therapy. including atazanavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jiroveci pneumonia, or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment. Bedistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. 5.12 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.13 Resistance/Cross-ResistanceVarious degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors [see Microbiology (12.4)]. ADVERSE REACTIONS ADVENSE REACTIONS
following adverse reactions are discussed in greater detail in other sections of the labeling:
cardiac conduction abnormalities [see Warnings and Precautions (5.1)]
rash [see Warnings and Precautions (5.2)]
hyperbility-binemia [see Warnings and Precautions (5.8)]
chronic kidney disease [see Warnings and Precautions (5.5)]
nephrolithiasis and cholelithiasis [see Warnings and Precautions (5.6)]

6.1 Clinical Trial Experience

Recause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse Reactions in Treatment-Naive Adult Patients The safety profile of atazanavir in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received atazanavir 300 mg with ritonavir 100 mg and 1089 patients received atazanavir 400 mg or higher (without ritonavir). Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive patients ng combination therapy including atazanavir 300 mg with ritonavir 100 mg and atazanavir 400 mg (without ritonavir) are presented in Tables 7 and 8, respectively Table 7: Selected Adverse Reactions of Moderate or Severe Intensity Reported in $\geq 2\%$ of Adult Treatment-Naive Patients, b Study Al424-138

Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF with emtricitabined opinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir DF with emtricitabine^d (n=437) **Digestive System** Jaundice/scleral icterus 12% Skin and Appendages None reported in this treatment arm. Includes events of possible, probable, certain, or unknown relationship to treatment regimen. Includes events of possible, probable, certain, or unknown relationship to treatment Based on the regimen containing atazanavir.

Median time on therapy.

As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily. Table 8: Selected Adverse Reactions^a of Moderate or Severe Intensity Reported in ≥ 2% of Adult Treatment-Naive Patients ^b Studies 4/424-034 A1424-007 and 4/424-008

	64 weeks ^c	1-034	Studies Al424-0	U7, -UU8
	Atazanavir	64 weeks ^c efavirenz 600 mg once daily + lamivudine + zidovudine ^e (n=401)	120 weeks ^{c,d} Atazanavir 400 mg once daily + stavudine + lamivudine or didanosine (n=279)	73 weeks ^{c,d} nelfinavir 750 mg TID or 1,250 mg BID + stavudine + lamivudine or didanosine (n=191)
Body as a Whole				
Headache	6%	6%	1%	2%
Digestive System				
lausea	14%	12%	6%	4%
aundice/scleral icterus	7%	*	7%	*
/omiting	4%	7%	3%	3%
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
lervous System				
nsomnia	3%	3%	<1%	*
Dizziness	2%	7%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
Skin and Appendages				
Rash	7%	10%	5%	1%

Table 9: Selected Adverse Reactions of Moderate or Severe

	Atazanavir/ritonav once daily + tenof (n=11	fovir DF + NRTI twic	48 weeks pinavir/ritonavir 400/100 mg e daily ^d + tenofovir DF + NRTI (n=118)
Body as a Whole			
Fever	2%		*
Digestive System			
Jaundice/scleral icterus			*
Diarrhea	3%		11%
Nausea	3%		2%
Nervous System	20/		40/
Depression	2%		<1%
Musculoskeletal System Myalgia	4%		*
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities in the percentages of adult tr at the percentages of adult tr at the percentages of and the percented in Tables 10 and	n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v l 11, respectively.	ts treated with combination vithout ritonavir) with Grad	n therapy including atazanavir 300 de 3 to 4 laboratory abnormalities
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities in the percentages of adult tr at the percentages of adult tr at the percentages of and the percented in Tables 10 and	tion. n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v l 11, respectively.	ts treated with combination without ritonavir) with Grad ties Reported in ≥2% of Ad	de 3 to 4 laboratory abnormalities
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr ith ritonavir 100 mg and esented in Tables 10 and able 10: Grade 3 to 4 L:	tion. n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit	ts treated with combination vithout ritonavir) with Grad	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks ^b lopinavir 400 mg with ritonavir 100 mg (twice daily
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 Li Al424-138	tion. n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit	ts treated with combination without ritonavir) with Gracties Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitabine
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 L: Al424-138 Variable	tion. n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit	ts treated with combination without ritonavir) with Gracties Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitabine
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 Li Al424-138 Variable Chemistry	tion. n Treatment-Naive Pareatment-naive patien atazanavir 400 mg (v 111, respectively, aboratory Abnormalit Limit ^d High	ts treated with combination without ritonavir) with Grac dies Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c (n=441)	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily DF and tenofovir DF with emtricitabine (n=437)
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 Li Variable Chemistry SGOT/AST	tion. n Treatment-Naive Pa reatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit Limit ^d High ≥5.1 × ULN	ts treated with combination without ritonavir) with Grac dies Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c (n=441)	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitabine (n=437)
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i ne percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and able 10: Grade 3 to 4 Li Al424-138 Variable Chemistry SGOT/AST SGPT/ALT	ition. n Treatment-Naive Pareatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit Limit ^d High ≥5.1 × ULN ≥5.1 × ULN	ts treated with combination without ritonavir) with Grac dies Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c (n=441) 3% 3%	de 3 to 4 laboratory abnormalities lult Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitabine (n=437) 1% 2%
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i the percentages of adult tr tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 Li Al424-138 Variable Chemistry SGOT/AST SGPT/ALT Total Bilirubin	ition. n Treatment-Naive Pareatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit Limit ^d High ≥5.1 × ULN ≥5.1 × ULN ≥2.6 × ULN	ts treated with combination without ritonavir) with Grac dies Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c (n=441) 3% 3% 44%	de 3 to 4 laboratory abnormalities luit Treatment-Naive Patients, a Str 96 weeks b lopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitabline c (n=437) 1% 2% <1%
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities i the percentages of adult in tith ritonavir 100 mg and esented in Tables 10 and tible 10: Grade 3 to 4 Li Variable Chemistry SGOT/AST SGPT/ALT Total Bilirubin Lipase	ition. n Treatment-Naive Pareatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit Limit ^d High ≥5.1 x ULN ≥2.6 x ULN ≥2.1 x ULN	ts treated with combination without ritonavir) with Grac ties Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ^c (n=441) 3% 3% 44% 2%	de 3 to 4 laboratory abnormalities Jult Treatment-Naive Patients, a Str Jopinavir 400 mg with ritonavir 100 mg (twice daily and tenofovir DF with emtricitablines (n=437) 1% 2% <1% 2%
Median time on therapy. As a fixed-dose combinat aboratory Abnormalities is the percentages of adult tr tith ritonavir 100 mg and resented in Tables 10 and able 10: Grade 3 to 4 Li Variable Chemistry SGOT/AST SGPT/ALT Total Bilirubin Lipase Creatine Kinase	ition. n Treatment-Naive Pareatment-naive patien atazanavir 400 mg (v 111, respectively. aboratory Abnormalit Limit ^d High ≥5.1 × ULN ≥2.6 × ULN ≥2.1 × ULN ≥5.1 × ULN	ts treated with combination without ritonavir) with Grac ties Reported in ≥2% of Ad 96 weeks ^b Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine ² (n=441) 3% 3% 44% 2% 8%	de 3 to 4 laboratory abnormalities State

	Creatine F	Kinase ≥	5.1 × ULN	8%	7	%
	Total Cho	lesterol ≥	240 mg/dL	11%	25	5%
	Hematolog	Jy	Low			
Neutrophils <75		i0 cells/mm ³	5%	2	%	
a b c d	Median time As a fixed-do ULN = upper able 11: Gra	ose combińation: r limit of normal. de 3 to 4 Laborat	300 mg tenofovir DF		oine once daily.	Patients, ^a Studies
-			Study AI42	4-034	Studies Al424-00	7, -008
	factable.	1:14	64 weeks ^b Atazanavir 400 mg once daily +lamivudine +zidovudine ^a (n=404)	64 weeks ^b efavirenz 600 mg once daily +lamivudine +zidovudine ^e (n=401)	120 weeks ^{h,c} Atazanavir 400 mg once daily +stavudine +lamivudine or +stavudine +didanosine (n=279)	73 weeks ^{b,c} nelfinavir 750 mg TID or 1,250 mg BID +stavudine +lamivudine or +stavudine +didanosine
_	/ariable	Limit ^d			(2)	(n=191)
0	Chemistry	<u>High</u>				
5	GOT/AST	≥5.1 × ULN	2%	2%	7%	5%
S	GPT/ALT	≥5.1 × ULN	4%	3%	9%	7%
Т	otal Bilirubin	\geq 2.6 × ULN	35%	<1%	47%	3%
P	lmylase	≥2.1 × ULN	*	*	14%	10%
L	.ipase	\geq 2.1 × ULN	<1%	1%	4%	5%
-	Ceatine Kinase		6%	6%	11%	9%
	otal Cholesterol	≥240 mg/dL	6%	24%	19%	48%
_	riglycerides	≥751 mg/dL	<1%	3%	4%	2%
H	lematology	Low				
H	lemoglobin	<8 g/dL	5%	3%	<1%	4%
Ν	leutrophils	$<750 \text{ cells/mm}^3$	7%	9%	3%	7%
a b c d e	Based on regir Median time o Includes long- ULN = upper li As a fixed-dos	term follow-up. imit of normal. e combination: 1:		•	vice daily.	
٠.		=====		-		

Change in Lipids from Baseline in Treatment-Naive Patients										
For Study Al424-138 and Study Al424-034, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Tables 12 and 13, respectively.										
Table 12: Lipid Values, Mean Change from Baseline, Study Al424-138										
	Baseline			r/ritonavi		Baseline		opinavir/r		
			ek 48		k 96	ma/dl	Week 48		Week 96	
	mg/dL (n=428°)	mg/dL (n=372°)	Change ^d (n=372 ^e)	mg/dL (n=342°)	Change ^d (n=342 ^e)	(n_/2/e)	mg/dL (n=335°)	Change ^d (n=335°)	mg/dL (n=291°)	Change ^d (n=291 ^e)
LDL-Cholesterol ^f	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol ^f	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total-Cholesterol ^f	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides ^f	126	145	+15%	140	+13%	129	194	+52%	184	+50%

Atazanavir 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily. Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the atazanavir /ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the atazanavir/ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the atazanavir/ritonavir arm. Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir DF, 200 mg emtricitabine once daily. 200 mg emtricitabine once daily.

The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean patients. Number of patients with LDL-cholesterol measured. Table 13: Lipid Values, Mean Change from Baseline, Study Al424-034

		Atazanavir ^{a,b} /ri		efavire	nz ^{b,c}	
	Baseline mg/dL (n=383°)	mg/dL Change ^d mg		Baseline mg/dL (n=378°)	Week 48 mg/dL (n=264°)	Week 48 Change ^d (n=253°)
LDL-Cholesterol ^f	98	98	+1%	98	114	+18%
HDL-Cholesterol	39	43	+13%	38	46	+24%
Total Cholesterol	164	168	+2%	162	195	+21%
Triglycerides ^f	138	124	-9%	129	168	+23%
atazanavir arm. Efavirenz 600 mg o daily. The change from ba and Week 48 values	aseline is the most a si	ean of within-p mple difference	atient changes e of the baselir	s from baselin	e for patients wi	th both basel
Number of patients Fasting.	WILLI LDL-CHOIC	SECTOT THEASURE	su.			
aboratory Abnormaliti	es in Treatment	t-Experienced F	Patients			
he percentages of tazanavir/ritonavir with						erapy includ

					48 weeks	S _p		48 we	eks ^b	
Table 14:	Grade 3 to Study AI42		ratory Abnor	malities R	eported in	≥ 2 % of <i>i</i>	Adult	Treatment-Exp	erienced	l Patients,
	entages of ritonavir wit							combination Table 14.	therapy	including
Laboratory	Abiloillialla	163 111 111	catilicit Exp	GIIGIIGGU I C	ationto					

Laboratory Abnormaliti									dose of midazolam is adn of oral midazolam with ataz
The percentages of atazanavir/ritonavir with Table 14: Grade 3 to Study Al42	h Grade 3 to 4 la 4 Laboratory A l	aboratory abi	ormalities are p	resented in	Table 14.	-	Calcium channel blockers: diltiazem	↑ diltiazem and desacetyl- diltiazem	Caution is warranted. A di 50% should be considerecommended. Coadminis with diltiazem has not bee
			48 weeks ^b Atazanavir/ritonavir 300/100 mg once daily + 4		48 weeks ^b lopinavir/ritonavir 400/100 mg twice daily ^d +		felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channe blocker	Caution is warranted. Do channel blocker should be is recommended.
Variable	Limit		enofovir DF + Ni (n=119)		tenofovir DF + NRTI (n=118)		Endothelin receptor antagonists: Bosentan	↓ atazanavir ↑ bosentan	Plasma concentrations of when bosentan is adminis ritonavir. Coadministration without ritonavir is not rec
Chemistry	<u>High</u>								Coadministration of bos
SGOT/AST	≥5.1 × UL		3%		3%				atazanavir/ritonavir:
SGPT/ALT	≥5.1 × UL		4%		3%				For patients who have beer for at least 10 days, start be
Total Bilirubin	≥2.6 × UL		49%		<1%				or every other day base
Lipase	≥2.1 × UL		5%		6%				Coadministration of at patients on bosentan:
Creatine Kinase	≥5.1 × UL		8%		8%				Discontinue bosentan at le
Total Cholesterol	≥240 mg/		25%		26%				atazanavir /ritonavir. At
Triglycerides	≥751 mg/		8%		12%				atazanavir /ritonavir, resur daily or every other day ba
Glucose	≥251 mg/	/dL	5%		<1%		HMG-CoA reductase inhibitors:	↑ atorvastatin	Titrate atorvastatin dose
Hematology	Low						atorvastatin, rosuvastatin	↑ rosuvastatin	necessary dose. Rosuvasi
Platelets	<50,000 cells		2%		3%				10 mg/day. The risk rhabdomyolysis, may be i
Neutrophils Based on regimen(s	<750 cells/n		7%		8%				inhibitors, including atazar with these drugs.
Median time on the ULN = upper limit of As a fixed-dose con Change in Lipids from For Study Al424-045, cl	f normal. nbination. <i>Baseline in Trea</i> l			abalastaral	total abalactoral	and triphyporidae	H2-Receptor antagonists	↓ atazanavir	Plasma concentrations of decreased when atazana: administered simultaneou twice daily in adults, will therapeutic effect and d
are shown in Table 15 lopinavir/ritonavir. How Table 15: Lipid Value	. The observed ever, the clinica	magnitude of si	of dyslipidemia uch findings has	was less wi not been de	th atazanavir/rit				In treatment-naive adult µ Atazanavir 300 mg with rito food should be administere
		Atazanavir/r	itonavir ^{a,b}		lopinavir/ri	tonavir ^{b,c}			at least 10 hours after,
	Baseline	Week 48	Week 48	Baseline	Week 48	Week 48			antagonist (H2RA). An
	mg/dL (n=111°)	mg/dL (n=75°)	Change ^d (n=74°)	mg/dL (n=108°)	mg/dL (n=76°)	Change ^d (n=73°)			famotidine 20 mg once da to famotidine 40 mg twi atazanavir 300 mg
LDL-Cholesterol ^f	108	98	-10%	104	103	+1%			with ritonavir 100 mg in tr
HDL-Cholesterol	40	39	-7%	39	41	+2%			For notionto unable to tale
Total Cholesterol	188	170	-8%	181	187	+6%			For patients unable to tole mg once daily with food sh
Triglycerides ^f	215	161	-4%	196	224	+30%			2 hours before and at least
 Atazanavir 300 mg Values obtained afte serum lipid-reducin /ritonavir arm. Thro treatment arm and 8 	er initiation of se g agents were us ough Week 48,	rum lipid-red sed in 4% in serum lipid-	ucing agents we the lopinavir/rito reducing agents	re not includ navir treatm	ent arm and 4%	in the Atazanavir			H2RA. No single dose of the comparable to famotidine dose should not exceed a d 40 mg. The use of atazanavi women is not recommend

Antimycobacterials: rifabutin

Adverse Reactions in Pediatric Patients: Atazanavir Capsules		administ hours af
The safety and tolerability of atazanavir capsules with and without ritonavir have been established in pediatric patients at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A.		Atazar (all as
The safety profile of atazanavir in pediatric patients (6 to less than 18 years of age) taking the capsule formulation was generally similar to that observed in clinical studies of atazanavir in adults. The most common Grade 2 to 4 adverse events (≥5%, regardless of causality) reported in pediatric patients were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), asal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in <2% of patients. The most common Grade 3 to 4 laboratory abnormalities occurring in pediatric patients taking the capsule formulation were elevation of total bilirubin (≥3.2 mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3 to 4 laboratory abnormalities occurred with a frequency of less than 3%.		Atazar (all as tenofo Ataza (all as tenofo the serecom and the DF and the serecom and the description and
Adverse Reactions in Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus	Lathian Laster dial	-
In Study Al424-138, 60 patients treated with atazanavir/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir DF-emtricitabine, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 10% (6/60) of the atazanavir/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (6/60) of the atazanavir/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.	↑norgestimatec	Use with atazanavi If an ora plus rit contrace If atazan contrace
In Study Al424-045, 20 patients treated with atazanavir/ritonavir 300 mg/100 mg once daily, and 18 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 25% (5/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (2/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.		ethinyl e Potentia progeste in concer
efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. ALT levels >5		and cou dyslipide
times ULN developed in 15% of the atazanavir-treated patients, 14% of the efavirenz-treated patients, and 17%		Coadmir

with lopinavir/ritonavir 400 mg/100 mg twice daily, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 25% (5/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (2/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.
In Studies Al424-008 and Al424-034, 74 patients treated with 400 mg of atazanavir once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 15% of the atazanavir-treated patients, 14% of the feativernz-treated patients, and 17% of the nelfinavir-treated patients. AST levels >5 times ULN developed in 9% of the atazanavir-treated patients, 55% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. Within atazanavir and control regimens, no difference in frequency of bilirubin elevations was noted between seropositive and seronegative patients [see Warnings and Precautions (5.8)].
6.2 Postmarketing Experience The following events have been identified during postmarketing use of atazanavir. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Body as a Whole: edema
Cardiovascular System: second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation [see Warnings and Precautions (5.1)]
Gastrointestinal System: pancreatitis
Hepatic System: hepatic function abnormalities
Hepatobiliary Disorders: cholelithiasis [see Warnings and Precautions (5.6)], cholecystitis, cholestasis
Metabolic System and Nutrition Disorders: diabetes mellitus, hyperglycemia [see Warnings and Precautions (5.9)]
Musculoskeletal System: arthralgia
Renal System: nephrolithiasis [see Warnings and Precautions (5.6)], interstitial nephritis, granulomatous interstitial nephritis, chronic kidney disease [see Warnings and Precautions (5.5)]

Skin and Appendages: alopecia, maculopapular rash [see Contraindications (4) and Warnings and Precautions (5.2)], pruritus, angioedema 7 DRUG INTERACTIONS
7.1 Potential for Atazanawir to Affect Other Drugs
Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of atazanavir and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or Atazanavir is a weak inhibitor of CYP2C8. Use of atazanavir without ritonavir is not recommended when coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide) When atazanavir with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected [see Clinical Pharmacology, Table 22 (12.3)]. The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when atazanavir is 7.2 Potential for Other Drugs to Affect Atazanavi

coadministered with ritonavir. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir. Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce atazanavir therapeutic effect. Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H2-receptor antagonists are administered with atazanavir [see Dosage and Administration (2.3, 2.4, and 2.6)]. 7.3 Established and Other Potentially Significant Drug Interactions Table 16 provides dosing recommendations in adults as a result of drug interactions with atazanavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy. Table 16: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies^a or Predicted Interactions (Information in the

Concomitant DrugClass: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric-coated (EC) capsules	↓atazanavir ↓didanosine	Coadministration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, atazanavir and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors:tenofovir disoproxil fumarate (DF)	↓atazanavir †tenofovir	Tenofovir DF may decrease the AUC and C _{mo} of atazanavir. When coadministered with tenofovir DF in adults, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir DF 300 mg (all as a single daily dose with food). Atazanavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse reactions, including renal disorders. Patients receiving atazanavir and tenofovir DF should be monitored for tenofovir-associated adverse reactions. For pregnant women taking atazanavir with ritonavir and tenofovir DF, see Dosage and Administration (2.6).
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓atazanavir	Efavirenz decreases atazanavir exposure. In treatment-naive adult patients: In treatment-naive adult patients: If atazanavir is combined with efavirenz, atazanavir 400 mg (two 200-mg capsules) should be administered with ritonavir 100 mg simultaneously once daily with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. In treatment-experienced adult patients: Coadministration of atazanavir with efavirenz in treatment-experienced patients is not recommended due to decreased atazanavir exposure.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1,200 mg coadministered with atzanavir 400 mg and tenofovir DF 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy [see Clinical Studies (14.2)].
Ritonavir	↑atazanavir	If atazanavir is coadministered with ritonavir, it is recommended that atazanavir 300 mg once daily be given with ritonavir 100 mg once daily with food in adults. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.
Others	↑other protease inhibitor	Although not studied, the coadministration of atazanavir/ritonavir and an additional protease inhibitor would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
HCV Antiviral Agents		
Protease Inhibitors: boceprevir	↓atazanavir ↓ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir/ritonavir and boceprevir is not recommended.
sofosbuvir, velpatasvir, voxilaprevir	↑voxilaprevir	Coadministration with atazanavir is not recommended.
Other Agents		D. J. and
Antacids and buffered medications	↓atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.

		given with ritonavir 100 mg once daily with food in adults. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.
Others	↑other protease inhibitor	Although not studied, the coadministration of atazanavir/intonavir and an additional protease inhibitor would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
HCV Antiviral Agents		
Protease Inhibitors: boceprevir	↓atazanavir ↓ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir/ritonavir and boceprevir is not recommended.
sofosbuvir, velpatasvir, voxilaprevir	↑voxilaprevir	Coadministration with atazanavir is not recommended.
Other Agents		
Antacids and buffered medications	↓atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), quinidine	†amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
Anticoagulants: warfarin	↑warfarin	Coadministration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that International Normalized Ratio (INR) be monitored.
Antidepressants: tricyclic antidepressants	†tricyclic antidepressants	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
Trazodone	↑trazodone	Concomitant use of trazodone and atazanavir with or without ritonavir may increase plasma concentrations of trazodone. Nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYPSA4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Antiepileptics: carbamazepine	↓atazanavir ↑carbamazepine	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with atazanavir without ritonavir. Coadministration of carbamazepine and atazanavir without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with atazanavir/ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
phenytoin, phenobarbital	↓atazanavir ↓phenytoin ↓phenobarbital	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with atazanavir without ritonavir. Coadministration of phenytoin or phenobarbital and atazanavir without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When atazanavir with ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.
Lamotrigine	↓lamotrigine	Coadministration of lamotrigine and atazanavir with ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with atazanavir and ritonavir. Coadministration of lamotrigine and atazanavir without ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with atazanavir without ritonavir.
Antifungals: ketoconazole, itraconazole	Atazanavir / ritonavir: ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and Cmax). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and irraconazole (>200 mg/day) should be used cautiously with atazanavir/ritonavir.
Voriconazole	Atazanavir /ritonavir in subjects with a functional CYP2C19 allele: \$\times\$ voriconazole \$\times\$ atazanavir Atazanavir	The use of voriconazole in patients receiving atazanavir/ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole associated adverse reactions and loss of either voriconazole or atazanavir efficacy during the coadministration of voriconazole and atazanavir/ritonavir. Coadministration of voriconazole

ritonavir in subjects with a functional CYP2C19 allele: ↑ voriconazole ↓ atazanavir	with atazanavir (without ritonavir) may affect atazanavir concentrations; however, no data are available.
↑ colchicine	The coadministration of atazanavir colchicine in patients with renal or hepatic impairment is not recommended.
	Recommended adult dosage of colchicine when administered with alazanavir: Treatment of gout flares: 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of tamilial Mediterranean tever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).

Through Week 48, se									Ose of furasidone is contrallidicated.
atazanavir arm. Efavirenz 600 mg on							Benzodiazepines: parenterally administered midazolam ^b	↑ midazolam	Concomitant use of parenteral midazolam with atazanavir
daily.	,				,		aummistereu midazoiam-		may increase plasma concentrations of midazolam. Coadministration should be done in a setting which
d The change from bas and Week 48 values						th both baseline			ensures close clinical monitoring and appropriate medical
Number of patients v				c allu vvcck	40 Illeali values.				management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam
[†] Fasting.									should be considered, especially if more than a single dose of midazolam is administered. Coadministration
Laboratory Abnormalitie		-							of oral midazolam with atazanavir is CONTRAINDICATED.
The percentages of a atazanavir/ritonavir with						erapy including	Calcium channel blockers:	↑ diltiazem and	Caution is warranted. A dose reduction of diltiazem by
Table 14: Grade 3 to 4		-	-			enced Patients.	diltiazem	desacetyl- diltiazem	50% should be considered. ECG monitoring is recommended. Coadministration of atazanavir /ritonavir
Study AI424						,			with diltiazem has not been studied.
			48 weeks ^b		48 weeks	b	felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring
			azanavir/ritona 100 mg once da		lopinavir/rito 400/100 mg twic		and verapanni	DIOCKCI	is recommended.
			nofovir DF + NF		tenofovir DF +	NRTI	Endotholia recentor entegonistes	Latazanovir	Plasma concentrations of atazanavir may be decreased
Variable	Limit ^c		(n=119)		(n=1	118)	Endothelin receptor antagonists: Bosentan	↓ atazanavir ↑ bosentan	when bosentan is administered with atazanavir without ritonavir. Coadministration of bosentan and atazanavir
Chemistry	High								without ritonavir is not recommended.
SGOT/AST	 ≥5.1 × UL	N	3%		3%				Coadministration of bosentan in adult patients on atazanavir/ritonavir:
SGPT/ALT	≥5.1 × UL		4%		3%				For patients who have been receiving atazanavir/ritonavir
Total Bilirubin	≥2.6 × UL	.N	49%		<1%				for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Lipase	≥2.1 × UL	.N	5%		6%				Coadministration of atazanavir/ritonavir in adult
Creatine Kinase	≥5.1 × UL	.N	8%		8%				patients on bosentan:
Total Cholesterol	≥240 mg/	/dL	25%		26%				Discontinue bosentan at least 36 hours before starting atazanavir /ritonavir. At least 10 days after starting
Triglycerides	≥751 mg/	/dL	8%		12%				atazanavir /ritonavir, resume bosentan at 62.5 mg once
Glucose	≥251 mg/	/dL	5%		<1%		IMC CoA raduatasa inhihitara	↑ otopyoototin	daily or every other day based on individual tolerability. Titrate atorvastatin dose carefully and use the lowest
Hematology	Low						HMG-CoA reductase inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	necessary dose. Rosuvastatin dose should not exceed
Platelets	<50,000 cells/		2%		3%				10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease
Neutrophils	<750 cells/m		7%		8%				inhibitors, including atazanavir, are used in combination
 Based on regimen(s) Median time on thera 		zanavir.					UO Bassatas antennaista	Laterania	with these drugs.
 ULN = upper limit of 	normal.						H2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg once daily was
d As a fixed-dose com									administered simultaneously with famotidine 40 mg
Change in Lipids from B		-		-111	****				twice daily in adults, which may result in loss of therapeutic effect and development of resistance.
For Study Al424-045, cha are shown in Table 15.									In treatment-naive adult patients:
lopinavir/ritonavir. Howe					emonstrated.				Atazanavir 300 mg with ritonavir 100 mg once daily with
Table 15: Lipid Values		Atazanavir/rit		4-040	lopinavir/rit	onavir ^{b,c}			food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2 -receptor
	Baseline	Week 48	Week 48	Baseline	Week 48	Week 48			antagonist (H2RA). An H2RA dose comparable to
	mg/dL (n=111°)	mg/dL	Changed	mg/dL	mg/dL	Change ^d			famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with
I DI Oli I I I I I I		(n=75°)	(n=74e)	(n=108°)	(n=76°)	(n=73°)			atazanavir 300 mg
LDL-Cholesterol [†] HDL-Cholesterol	108 40	98 39	-10% -7%	104 39	103 41	+1% +2%			with ritonavir 100 mg in treatment-naive patients. OR
Total Cholesterol	188	170	-8%	181	187	+6%			For patients unable to tolerate ritonavir, atazanavir 400
Triglycerides ^f	215	161	-4%	196	224	+30%			mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the
a Atazanavir 300 mg o	nce daily + rito	navir + tenofo	vir DF + 1 NRTI						H2RA. No single dose of the H2RA should exceed a dose
b Values obtained after	r initiation of ser	rum lipid-redu	icing agents we	re not includ	ded in these analy	ses. At baseline,			comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine
serum lipid-reducing /ritonavir arm. Thro	agents were us ugh Week 48, s	sea in 4% in tr serum lipid-re	educing agents	were used	ient arm and 4% in 19% in the lo	n the Atazanavir pinavir/ritonavir			40 mg. The use of atazanavir without ritonavir in pregnant
treatment arm and 8°	% in the atazan	avir/ritonavir a	arm.						women is not recommended.
 Lopinavir/ritonavir (4 The change from bas 				from baseli	ine for patients wi	th both baseline			In treatment-experienced adult patients: Whenever an H2RA is given to a patient receiving
and Week 48 valu				he baselin	e and Week 48	mean values.			atazanavir with ritonavir, the H2RA dose should not
 Number of patients v f Fasting. 	VITTI LDL-CHOIES	steroi measure	ea.						exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir and ritonavir doses should be
Adverse Reactions in Pe	diatric Patients	: Atazanavir C	apsules						administered simultaneously with, and/or at least 10
The safety and tolerabil						hed in pediatric			hours after, the dose of the H2RA. • Atazanavir 300 mg with ritonavir 100 mg once daily
patients at least 6 years									(all as a single dose with food) if taken with an H2RA. Atazanavir 400 mg with ritonavir 100 mg once daily
The safety profile of ataz was generally similar to									(all as a single dose with food) if taken with both
to 4 adverse events (≥	5%, regardless	of causality) reported in p	ediatric pat	tients were coug	h (21%), fever			tenofovir DF and an H2RA. • Atazanavir 400 mg with ritonavir 100 mg once daily
(18%), jaundice/scleral edema (7%), extremity page 1									(all as a single dose with food) if taken with either
(6%). Asymptomatic ser	cond-degree at	rioventricular	block was repo	orted in <29	% of patients. The	most common			tenofovir DF or an H2RA for pregnant women during the second and third trimester. Atazanavir is not
Grade 3 to 4 laboratory a of total bilirubin (≥3.2 m									recommended for pregnant women during the second
abnormalities occurred v					,				and third trimester taking atazanavir with both tenofovir DF and an H2RA.
Adverse Reactions in Pa	tients Co-Infec	ted with Hepat	titis B and/or H	epatitis C Vi	irus		Hormonal contraceptives:	↓ethinyl estradiol	
In Study Al424-138, 60 p with lopinavir/ritonavir							ethinyl estradiol and	↑norgestimatec	Use with caution if coadministration of atazanavir or atazanavir /ritonavir with oral contraceptives is considered.
seropositive for hepatit	is B and/or C a	at study entry	. ALT levels >5	times ULN	I developed in 10	% (6/60) of the	norgestimate or norethindrone		If an oral contraceptive is administered with atazanavir
atazanavir/ritonavir-treat ULN developed in 10% (plus ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol.
treated patients.	0,00,01 110 414	Zunuvn/ntonuv	iii troutou putio	ito una non	0 (0/00) 01 110 10	pinavii/iitonavii		↑ethinyl estradiol	If atazanavir is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of
In Study Al424-045, 20 p								↑norethindroned	ethinyl estradiol.
with lopinavir/ritonavir ALT levels >5 times UL	400 mg/100 m N developed in	ng twice daily, n 25% (5/20)	, were seropos of the atazana	sitive for he /ir/ritonavir-	patitis B and/or C -treated patients	at study entry. and 6% (1/18)			Potential safety risks include substantial increases in
of the lopinavir/ritonavir-	treated patients.	. AST levels >5	times ULN deve	eloped in 109					progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown
treated patients and 6% In Studies AI424-008 ar	. ,	-	-		novir once deily	E0 who received			and could increase the risk of insulin resistance,
efavirenz, and 12 who re	eceived nelfinav	ir were serop	ositive for hepa	titis B and/o	or C at study entr	y. ALT levels >5			dyslipidemia, and acne.
times ULN developed in of the nelfinavir-treated									Coadministration of atazanavir or atazanavir/ritonavir with other hormonal contraceptives (eg. contraceptive
5% of the efavirenz-tre	eated patients,	and 17% of the	he nelfinavir-tre	eated patien	ıts. Within atazan	avir and control			patch, contraceptive vaginal ring, or injectable
regimens, no difference patients [see Warnings a			evations was n	oted betwee	en seropositive a	nd seronegative			contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate,
6.2 Postmarketing Ex		(0.0/].							or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception
The following events ha	ve been identif								are recommended.
reported voluntarily from or establish a causal rela			e, it is not alway	s possible t	to reliably estimate	e ineir trequency	Immunosuppressants:	↑immuno-	Therapeutic concentration monitoring is recommended
Body as a Whole: edema		J . p					cyclosporine, sirolimus, tacrolimus	suppressants	for these immunosuppressants when coadministered with atazanavir.
Cardiovascular System prolongation [see Warni			, third-degree	AV block,	left bundle bra	inch block, QTc	Inhaled beta agonist:	↑salmeterol	Coadministration of salmeterol with atazanavir is not
Gastrointestinal System:		(0.1)]					Salmeterol		recommended.
Hepatic System: hepatic f									Concomitant use of salmeterol and atazanavir may result in increased risk of cardiovascular adverse reactions
Hepatobiliary Disorder					.6)], cholecystit e <i>Warninos and P</i> :				associated with salmeterol, including QT prolongation,

A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse

Initiation of atazanavir with ritonavir in patients taking

is necessary, reduce the quetiapine dose to 1/6 of the

irrent dose and monitor for quetiapine-associate

adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction

Initiation of quetiapine in patients taking atazanavir

Refer to the quetiapine prescribing information for initial

Atazanavir without ritonavir
If coadministration is necessary, reduce the lurasidone
dose. Refer to the lurasidone prescribing information
for concomitant use with moderate CYP3A4 inhibitors.

increases in quetiapine exposures. If coadn

dosing and titration of quetiapine.

Use of lurasidone is contraindicated.

with ritonavir:

Inhaled/nasal steroid: fluticasone	Atazanavir †fluticasone Atazanavir/ ritonavir †fluticasone	Concomitant use of fluticasone propionate and atazanavir (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Concomitant use of fluticasone propionate and atazanavir /ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate coadministration of fluticasone propionate and atazanavir/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects [see Warnings and Precautions (5.1)].
Macrolide antibiotics: clarithromycin	↑clarithromycin ↓ 14-0H clarithromycin ↑atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with atazanavir In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to Mycobacterium avium complex. Coadministration of atazanavir/ritonavir with clarithromycin has not been studied.
Opioids: Buprenorphine	†buprenorphine †norbupre- norphine	Coadministration of buprenorphine and atazanavir with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of atazanavir plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations. The coadministration of atazanavir and buprenorphine without ritonavir is not recommended.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):
		Use of REVATIO® (sildenafil) for the treatment of pulmonary hypertension (PAH) is contraindicated with atazanavir [see Contraindications (4)].
		The following dose adjustments are recommended for the use of ADCIRCA® (tadalafil) with atazanavir:
		Coadministration of ADCIRCA® in patients on atazanavir (with or without ritonavir): • For patients receiving atazanavir (with or without ritonavir) for at least one week, start ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Coadministration of atazanavir (with or without ritonavir) in patients on ADCIRCA®. • Avoid the use of ADCIRCA® when starting atazanavir (with or without ritonavir). Stop ADCIRCA® at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir) without without ritonavir).

palpitations, and sinus tachycardia.

		ADCIRCA [®] at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume ADCIRCA [®] at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.
		Use of PDE5 inhibitors for erectile dysfunction: Use VIAGRA® (sildenafil) with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use CIALIS® (tadalafil) with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.
		Atazanavir/ritonavir: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse reactions.
		Atazanavir: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse reactions.
Proton-pump inhibitors: omeprazole	↓atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg or atazanavir 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily in adults, which may result in loss of therapeutic effect and development of resistance.
		In treatment-naive adult patients: The proton-pump inhibitor (PPI) dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the atazanavir 300 mg with ritonavir 100 mg dose.
		In treatment-experienced adult patients: The use of PPIs in treatment-experienced patients receiving atazanavir is not recommended.
For magnitude of interactions so See Contraindications (4), Table In combination with atazanavir In combination with atazanavir	e 6 for orally admini 300 mg and ritonav	stered midazolam.

)	See Contraindications (4), Table 6 for orally administered midazolam.
	In combination with atazanavir 300 mg and ritonavir 100 mg once daily.
	In combination with atazanavir 400 mg once daily.
lo	4 Drugs with No Observed Interactions with Atazanavir clinically significant drug interactions were observed when atazanavir was coadministered with methadone, conazole, acetaminophen, atenolol, or the nucleoside reverse transcriptase inhibitors lamivudine or zidovudine ee Clinical Pharmacology, Tables 21 and 22 (12.3)].
1.1	USE IN SPECIFIC POPULATIONS 1. Pregnancy

Risk Summary

Atazanavir has been evaluated in a limited number of women during pregnancy. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. No treatment-related malformations were observed in rats and rabbits, for which the atazanavir exposures were 0.7 to 1.2 times of those at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). When atazanavir was administered to

rats during pregnancy and throughout lactation, reversible neonatal growth retardation was observed [see Data]. Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

**Atazanavir must be administered with ritonavir in pregnant women.

**For pregnant patients, no dosage adjustment is required for atazanavir with the following exceptions:

**For treatment-experienced pregnant women during the second or third trimester, when atazanavir is coadministered with either an H2-receptor antagonist or tenofovir DF, atazanavir 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a atazanavir dose for use with both an H2-receptor antagonist and tenofovir DF in treatment-experienced pregnant women.

**No dosage adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery [see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)].

Maternal Adverse Reactions Maternal Adverse Reactions

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using atazanavir in combination with nucleoside analogues, which are associated with an increased risk of lactic acidosis syndrome. Hyperbilirubinemia occurs frequently in patients who take atazanavir [see Warnings and Precautions (5.8)], Advise pregnant women of the potential risks of lactic acidosis syndrome and hyperbilirubinemia All infants, including neonates exposed to atazanavir *in utero*, should be monitored for the development of severe hyperbilirubinemia during the first few days of life [see Data].

Human Data In clinical trial Al424-182, atazanavir/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 HIV-infected pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA less than 50 copies/mL at time of delivery. Six of 20 (30%) women on atazanavir/ritonavir 300/100 mg and 13 of 21 (62%) women on atazanavir/ritonavir 400/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times ULN). There were no cases of lactic acidosis observed in clinical trial Al424-182. Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12% to 19% of maternal concentrations. Among the 40 infants born to 40 HIV-infected pregnant women, all had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antitertoviral prophylactic treatment containing zidovudine. No evidence of severe hyperbilinemia (total bilirubin levels greater than 20 mg/dL) or acute or chronic bilirubin encephalopathy was observed among neonates in this study. However, 10/36 (28%) infants (6 greater than or equal to 38 weeks gestation and 4 less than 38 weeks gestation) had bilirubin levels of 4 mg/dL or greater within the first day of life.

Lack of ethnic diversity was a study limitation. In the study population, 33/40 (83%) infants were Black/African American, who have a lower incidence of neonatal hyperbilirubinemia than Caucasians and Asians. In addition women with Rh incompatibility were excluded, as well as women who had a previous infant who developed hemolytic disease and/or had neonatal pathologic jaundice (requiring phototherapy). Additionally, of the 38 infants who had glucose samples collected in the first day of life, 3 had adequately collected serum glucose samples with values of less than 40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Based on prospective reports from the APR of approximately 1,600 live births following exposure to atazanavir containing regimens (including 1,037 live births in infants exposed in the first trimester and 569 exposed in second/third trimesters), there was no difference between atazanavir and overall birth defects compared with the background birth defect rate. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2 to 4%. Animal Data In animal reproduction studies, there was no evidence of mortality or teratogenicity in offspring born to animals

in animal reproduction studies, there was no evidence of inortanity or teratogenicity in onspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In pre- and postnatal development studies in the rat, atazanavir caused neonatal growth retardation during lactation that reversed after weaning. Maternal drug exposure at this dose was 1.3 times the human exposure at the recommended clinical exposure. Minimal maternal toxicity occurred at this exposure level. 8.2 Lactation The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Atazanavir has been detected in human milk. No data are available regarding atazanavir effects on milk production. Atazanavir was present in the milk of lactating rats and was associated with neonatal growth retardation that reversed after weaning.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in breastfed

8.4 Pediatric Use Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 3 months of age and older weighing at least 5 kg. Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus [see Indications and Usage (1)]. All atazanavir contraindications, warnings, and precautions apply to pediatric patients [see Contraindications (4) and Warnings

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

• 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

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

decrease HIV-related illnesses.

 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 lifethreatening side effects or death when used with these medicines: o alfuzosin (UROXATRAL®) o cisapride (PROPULSID®) o elbasvir/grazoprevir (ZEPATIER®)

 ergotamine tartrate (CAFERGOT®, MIGERGOT®, ERGOMAR®, ERGOSTAT®, MEDIHALER®, Ergotamine, WIGRAINE®, WIGRETTES®) • dihydroergotamine mesylate (D.H.E. 45®, MIGRANAL®) methylergonovine (METHERGINE®) o glecaprevir/pibrentasvir (MAVYRET®)

o ergot medicines including:

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

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 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

• 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

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

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

away if you get symptoms of gallbladder problems which may 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 muscle pain diarrhea stomach-area pain diarrhea vomiting trouble sleeping depression numbness, tingling, fever or burning of hands or feet

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

General information about the safe and effective use of atazanavir 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,

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propylene glycol, shellac, strong ammonia solution, titanium

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

dioxide.

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, Al424-451, and Al424-39T [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. 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 Cma. 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 Attazanavir 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)].

iman 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 obser 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 CssHszNsO7.HzSO4 which corresponds to a molecular weight of 802.9

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

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)].

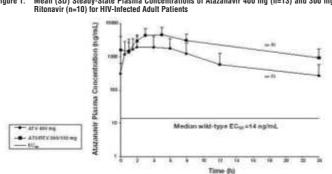
Caroliac Electrophysiology

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 (Al424-076), the mean (£SD) maximum change in PR interval from the predose value was 24 (£15) msec following oral dosing with one 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 (5.7)]. 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 he pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV- infected patients after dministration 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 300 mg with ritonavir 100 mg once daily 400 mg once daily

Parameter F	lealthy Subjects (n=14)	HIV-Infected Patients (n=13)	Healthy Subjects (n=28)	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 AUC (ng•h/mL)	2.5	2.0	2.7	3.0
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) C _{min} (ng/mL)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2) ^a	8.6 (2.3)
Geometric mean (CV%) 159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298)b	1441 (757)	862 (838)

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



Adazanavir 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 Food Effect

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 tration 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% companyed to the festion state. 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.

Metadonism
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 ¹⁴C-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} at multiple doses of 400 mg orice daily. The fleath attachanger Chasx Was 9% lower, AUC was 19% ingliert, and chasses were real 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 Cmax, 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 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_{10 tox}) 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)]. 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

ritonavir C_{max} ng/mL AUC ng•h/mL C_{min} ng/mL (mg) Geometric Mean (CV%) (CV%) (CV%) (CV%) 15 to <35 200/100 3.303 (86%) 37.235 (84%) 538 (99%) 2,980 (82%) 37,643 (83%) 653 (89%) 300/100 Pregnancy
The pharmacokinetic data from HIV-infected pregnant women receiving atazanavir capsules with ritonavir are Table 20: Steady-State Pharmacokinetics of Atazanavir with Ritonavir in HIV-Infected Pregnant Women in

	Ata	zanavir 300 mg with riton	avir 100 mg
Pharmacokinetic Parameter	2nd Trimester	3rd Trimester	Postpartumb
	(n=5 ^a)	(n=20)	(n=34)
C _{max} ng/mL	3,078.85	3,291.46	5,721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng•h/mL	2,7657.1	34,251.5	61,990.4
Geometric mean (CV%)	(43)	(43)	(32)
C _{min} ng/mL ^c	5,38.70	668.48	1,462.59
Geometric mean (CV%)	(46)	(50)	(45)

mpared to those observed historically in HIV-infected, non-pregnant patients Drug Interaction Data vir 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 6B-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, CYP286, 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 Rased on known metabolic profiles, clinically significant drug interactions are not expected between atazanavi 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 on the AUC, C _{max} , and C _r effect on atazanavir exp Atazanavir did not have tablet), stavudine, or flu		okinetic interactions. The oles 21 and 22. Neither or effect of atazanavir the exposures of didar on regarding clinical re	ne effects of coodidanosine EC noon didanosine loosine (when a commendations	administration or diltiazem ha EC or diltiazen dministered as s, see <i>Drug In</i> t	of atazanavir d a significant n exposures). s the buffered deractions (7).					
Drugs³ Coadministered Drug Dose/ Schedule Drug 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 (ddl) (buffered tablets) plus stavudine (d4T) ^b	ddl: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=31)	400 mg × 1 dose simultaneously with ddl and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)					
	ddl: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=32)	400 mg × 1 dose 1 h after ddl + 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)°	300 mg QD/ritonavir 100 mg QD, d 1-10 (n=46),d 11-20d (simultaneous	0.86 (0.79, 0.94)	0.82 (0.75,0.89	0.72 (0.64, 0.81)					

300 mg QD/ritonavir 100 mg QD/ tenofovir DF 300 mg

QD, d 1-10 (am) n=39), d 11-17 (am)

r 0.91 0.90 0.81 (0.84, 0.99) (0.82,0.98) (0.64, 0.81)

20 mg BID, d 11-17

Coadministered Drug	Coadministered Drug Dose/ Schedule	Atazanavir Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Paramete with/without Coadministered Drug;			
			C _{max} N	o Effect = 1.00	_	
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 (0.63,0.9	
	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 (0.63,0.8	
	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 (0.68,1.0	
grazoprevir/ elbasvir	grazoprevir 200 mg QD d 1 to 35 (n = 11) elbasvir 50 mg QD	100 mg QD 300 mg QD/ritonavir	1.12 (1.01, 1.24) 1.02	1.43 (1.30, 1.57) 1.07	1.23 (1.13, 1.3	
ketoconazole	d 1 to 35 (n = 8) 200 mg QD,	100 mg QD 400 mg QD, d 1 to 13	0.99	(0.98,1.17)	1.03	
nevirapine ^f ,9	d 7 to 13 (n=14) 200 mg BID, d 1 to 23 (n=23)	(n=14) 300 mg QD/ritonavir 100 mg QD, d 4 to 13, then 400 mg QD/ ritonavir 100 mg	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.53, 2.0 0.28 (0.20, 0.4 0.41 (0.27, 0.6	
omeprazole	40 mg QD, d 7 to12 (n=16)i	QD, d 14 to 23 (n=23)h 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	
	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, 0.2	
	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, 0.7	
	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, 0.8	
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, 1.8	
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, 0.0	
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.	
tenofovir DFº	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, 0.6	
	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, 1.1	
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, 0.9	
voriconazole	50 mg BID, d 2 to 3, 22 to 30;	300 mg/ ritonavir 100 mg	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.8	

atazanavir 300 mg and ritonavir 100 mg plus tenofovir DF 300mg. atazariavi sou mig and intonavir 100 mig plus tendovor in 2 souting.

Atazanavir /ritonavir/tendovir DF was administerd after a light meal.

Study was conducted in HIV-infected individuals.

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. respectively, for atazanavir/iritonavir 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/iritonavir 400/100 mg.

Parallel group design; n=23 for atazanavir/irtonavir plus nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

Omeprazole 40 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.

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).

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.

were similar when atazanavir 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours. Atazanavir 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted Atzanavir 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 C_{max} (26%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1 to 6).
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.
Note that similar results were observed in studies where administration of tenofovir DF and atazanavir was eparated by 12 hours. 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 footnote⁹). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir DF were:

C_{mx} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected in the conditional conditions and conditions are supported by the condition of the condition o

NA = not available. Table 22: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of 300 mg QD/

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-clarithrom ycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithro mycin: 0.30 (0.26, 0.34)	OH-clarithro mycin: 0.38
ddl (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)	, , ,
	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	2.25 (2.09, 2.16) desacetyl- diltiazem: 2.65	2.42 (2.14, 2.73) desacetyl- diltiazem: 2.21
ethinyl estradiol &	Ortho-Novum®	400 mg QD,	(2.44, 3.03) ethinyl	(2.45, 2.87) ethinyl	(2.02, 2.42) ethinyl
norethindrone ^c	7/7/7 QD, d 1-29 (n=19)	d 16-29 (n=19)	estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	estradiol: 1.48 (1.31, 1.68) norethind rone: 2.10 (1.68, 2.62)	estradiol: 1.91 (1.57, 2.33) norethind rone: 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)	1.85 (1.67, 2.05	norgesti mate: ^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, ¹ d 11-20 (n=3)	1.18 (0.94, 1.48) 25-0- desacetyl- rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-0- desacetyl- rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-0- 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) 25-0- desacetyl- rifabutin: 7.77 (6.13, 9.83)	1.48 ^m (1.19, 1.84) 25-0- desacetyl- rifabutin: 10.90 (8.14, 14.61)	1.40 ^m (1.05, 1.87) 25-0-d esacetyl- 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∘	↑3-foldº	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 G S-331007 1.05	1.40 (1.25, 1.57) sofosbuvir metabolite GS-331007 1.25	NA
			(0.99, 1.12)	(1.16, 1.36)	

	d 1-10 then 150 mg QD, d 11-20 (n=3)	d 11-20 (n=3)	1.48) 25-0- desacetyl- rifabutin: 8.20 (5.90, 11.40)	2.79) 25-0- desacetyl- rifabutin: 22.01 (15.97, 30.34)	5.96) 25-0- 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) 25-0- desacetyl- rifabutin: 7.77 (6.13, 9.83)	1.48 ^m (1.19, 1.84) 25-0- desacetyl- rifabutin: 10.90 (8.14, 14.61)	1.40 ^m (1.05, 1.87) 25-0-d esacetyl- 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-foldº	↑3-fold∘	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 G S-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)	
	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	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 0.96, 1.14) zidovudine	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine

Data provided are under fed conditions unless otherwise noted.

400 mg ddl EC and atazanavir were administered together with food on Days 8 and 19.

C Upon further dose normalization of ethinyl estradiol 25 mgo with atazanavir relative to ethinyl estradiol 35 mgg without atazanavir, the ratio of geometric means (90% confidence intervals) for Cmax, AUC, and Cmin were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively. U.82 (U.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 Cmax, AUC, and C. were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

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. 17-deacetyl norgestimate is the active component of norgestimate Fiffect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.
(R)-methadone is the active isomer of methadone. Study was conducted in HIV-infected individuals

0.95 | 1.00 | 0.82 (0.88, 1.02) | (0.97, 1.03) | (0.62, 1.08)

ubjects were treated with nevirapine prior to study entr Subjects were treated with nevirapine prior to sucuy enuy.

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. When compared to rifabutin 150 mg QD alone d1 to 10 (n=14). Total of rifabutin + 25-0-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69). azone used as a probe substrate for CYP2C8. Mean ratio (with/without coadministered drug). Tindicates an increase in rosuvastatin exposure. 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 7,9% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1,200 mg TID.

¹ Note that similar results were observed in a study where administration of tenofovir DF and atazanavir was

eparated by 12 hours. inistration 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 Antiviral Activity in Cell Culture Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human

Arazaravir eximins anti-riv-r activity with a filear IDV-r effective Contentiation (Egg) in the absence of intimates 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 EC₅₀ values above the EC₅₀ values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with PIs (amprenavir, indinavir, lopinavir, nelfinavir, intonavir, and saquinavir), NRTIS (delavirdine, etavirenz, and nevirapine), NTRIS (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, and zidovudine), the HIV-1 fusion inhibitor enfuviritide, and two compounds used in the treatment of viral heartitis. adefervir and irbaviring without enhanced cutothycisty. 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 the selected in cell culture by 5 months. The substitutions susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions n these HIV-1 viruses that contributed to ATV resistance include I50L, N88S, 184V, 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, rietnavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-

Study Al424-089 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 Al424-089: Comparison of Ritonavir Boosted atazanavir vs. Unboosted atazanavir: Randomized Patients Ritonavir 100 mg (n=95) Virologic Failure (≥50 copies/mL) at Week 96 15 (16%)

Virologic Failure with Genotypes and Phenotypes Data 0/5(0%)b 4/17 (24%)b Virologic Failure Isolates with ATV-resistance at Week 96 0/5(0%)b irologic Failure Isolates with I50L Emergence at 2/17 (12%)b Virologic Failure Isolates with Lamivudine 2/5 (40%)b Resistance at Week 96 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.
 Percentage of Virologic Failure Isolates with genotypic and phenotypic data.
 Mixture of ISOI/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant

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, I85IV, and L90M. The NRTI resistance-associated substitution and M34V also emerged on treatment in this isolate conferring emitticitating resistance. PI resistance-associated substitutions L10F. V32I, k43T, M46I, A711, G73S, [85I/V, and Ĺ90M. 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 110V, V111, 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. 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 necessing attactation 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), L33F, 673S, 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. efficacy of subsequently administered Pls.

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 Pls and displayed decreased susceptibility to multiple Pls. 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 V321, L33F/VI, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/TI, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other substitutions that developed on ATV/RTV treatment including E34K/AVQ, G48V, I84V, N8SS/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 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 Al424-397 (PRINCE) I) and Al424-451 (PRINCE II). 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 4.1,8, with an ATV cutoff of 2.2-fold change). Secondary PI resistance-associated amino acid substitutions also arose in the viruses of one subject

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 crossresistant 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 ATV and administration of the isolates resistant to attain the indicate the indicater of the isolates resistant to a transfer of the isolates and the isolates resistant to a magnenavir. 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 denotype/relenotype and virologic Outcome Analyses
Genotypic 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 Al424-045, As-Treated Analysis

Number and Type of Baseline PI Substitutions ²	Virologic Response = HIV RNA ATV/RTV (n=110)	<400 copies/mLb LPV/RTV (n=113)
3 or more primary PI substitutions including:		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)
154V/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)
184V/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)

 Results should be interpreted with caution because the subgroups were small.
 There were insufficient data (n<3) for PI substitutions V321, I47V, G48V, I50V, and F53L. The response rates of antiretroviral-experienced patients in Study Al424-045 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 Al424-045, As

Baseline Phenotype ^a	Virologic Response = HIV RNA <400 copies/m ATV/RTV LPV/RTV (n=111) (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)
	ure relative to the wild-type reference.	

NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ong-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mousi 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. 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 At the systemic unity exposure levels (Account of the Indianal Lats) of 2.3 (in lemma rats) times that of the Indiana clinical dose, (300 mg/day atazanavir boosted with 100 mg/day ritonavir) significant effects on matting, fertility or early embryonic development were not observed.

or early embryonic development were not observed.

14 CLINICAL STUDIES
14.1 Adult Patients without Prior Antiretroviral Therapy
Study Al424-138: 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 Al424-138 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/mm³ (range: 2 to 810 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.94 log₁₀ copies/mL (range: 2.60 to 5.88 log₁₀ copies/mL). Treatment response and outcomes through Week 96 are presented in Table 26.

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) witl tenofovir DF /emtricitabine (once daily)³ (n=437) 96 Weeks
Responder ^{b,c,d}	75%	68%
Virologic failuree	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%
As a fixed-dose combination: 300 mg ¹ Patients achieved HIV RNA <50 color Pre-specified ITT analysis at Week 48 u estimate: 1.7% [95% confidence intended of the setimate: 6.1% [95% confidence intended of the	pies/mL at Week 96. Roche Am Ising as-randomized cohort: ATV/R val: -3.8%, 7.1%]). Ising as-randomized cohort: ATV/R val: 0.3%, 12%]). chieve confirmed HIV RNA <50 co	iplicor®, v1.5 ultra-sensitive assay TV 78% and LPV/RTV 76% (differenc TV 74% and LPV/RTV 68% (differenc pies/mL through Week 96.

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/mm³ for the atazanavir /ritonavir arm and 273 cells/mm³ for the lopinavir/ritonavir arm. Study Al424-034: Atazanavir nonce daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study Al424-034 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 antirretroviral 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/mm³ (range: 64 to 1424 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.8 log_1opies/mL (range: 2.2 to 5.9 log_1o copies/mL). Treatment resonose and outcomes through Week 48 are presented in Table 27. 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 Al424-034)

efavirenz 600 mg once daily lamivudine + zidovudi (n=405) 67% (32%) 62% (37% Virologic failuret 20% 21% Rebound 17% Never sunnressed through Week 48 <1% Discontinued for other reasons^c 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.
 Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
 Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons. 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 etavirenz arms. The mean increase from baseline in CD4 + cell count was 176 cells/mm³ for the atazanavir arm and 160 cells/mm³ for the efavirenz arm. Study Al424-008: 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 Al424-008 was a 48-week, randomized, multicenter trial, blinded to dose of atazanavir, comparing atazanavir at two dos levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudin (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive patients. Patients had mean age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cel

count was 295 cells/mm3 (range: 4 to 1003 cells/mm3) 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

400 mg once daily + lamivudine + stavudine (n=181) 1.250 mg twice daily + line + stavu (n=91) 59% (38%) 67% (33% 27% Virologic failuret Rebound 14% Never suppressed through Week 48 10% <1% Discontinued due to adverse event Discontinued for other reasons: 10% 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 gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovi DF + one NRTI. Study Al424-045 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 caspules (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/mm³ (range: 14 to 1543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.4 log₁₀ copies/mL (range: 2.6 to 5.88 log₁₀ 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 Al424-045 was not large enough to reach a definitive conclusion that atazanavir/ritonavir and lopinavir/ritonavir are equivalent on the econdary efficacy outcome measure of proportions below the HIV RNA lower limit of quantification [see Microbiology, Tables 24 and 25 (12.4)].

HIV RNA Change from +0.12c Baseline (log₁₀ copies/mL)b 116 (-0.17, 0.41) CD4+ Change from

Baseline (cells/mm3)d

HIV RNA <400 copies/mLb 55%

HIV RNA <50 copies/mLb 38%

Percent of Patients

Respondinge

Table 29: Outcomes of Treatment Through Week 48 in Study Al424-045 (Patients with Prior Antiretrovira

(-19.6%, 5.4%) ¹ 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. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5. Protocol-defined primary efficacy outcome measure

57%

45%

-2.2%

(-14.8%, 10.5%)

-7.1%

d Based on patients with baseline and Week 48 CD4+ cell count measurements (atazanavir/ritonavir, n=85; looinavir/ritonavir, n=93). Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48 $No \ patients \ in \ the \ atazanavir/riton avir \ treatment \ arm \ and \ three \ patients \ in \ the \ lopin avir/riton avir \ treatment \ arm \ and \ three \ patients \ in \ the \ lopin avir/riton avir \ treatment \ arm \ a$ experienced a new-onset CDC Category C event during the study. In Study Al424-045, the mean change from baseline in plasma HIV-1 RNA for atazanavir 400 mg with saquinavir (n=115) was -1.55 log₁₀ 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/mm³. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA dol (-50) copies/mL was 38% (26%). In this study, coadministration of atazanavir and saquinavir did not provide adequate efficacy (see Drug Interactions (TVI)

[see Drug Interactions (7)]. Study Al424-045 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 log₁₀ copies/mL in the atazanavir treatment arm and -2.02 log₁₀ 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 actions with prior virologic failure and is not recommended for such patients. 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/mm³ in antiretroviral-naive patients and 220 cells/mm³ in antiretroviral-naive 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 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

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 usplied as follows

Bottle of 500 capsules

Cardon 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 Cardiac Conduction Abnormalities Cardiac Conduction Automatics
Inform patients that atzazinavir 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)].

Inform patients that asymptomatic elevations in indirect bilirubin have occurred in patients receiving atazanavi 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). 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)]. 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)].

Atazanavir capsules may lead to significant interaction with some drugs; therefore, advise patients to report the 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)]. 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

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)]. 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'.

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