Effect on

Clinical Comments

Issued: February 2020

---CONTRAINDICATIONS-

Hypersensitivity to lopinavir and ritonavir tablets (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme,

Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious

Co-administration with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with

---WARNINGS AND PRECAUTIONS-

The concomitant use of lopinavir and ritonavir and certain other drugs may result in known or potentially significant drug interactions.

Toxicity in preterm neonates: lopinavir and ritonavir oral solution should not be used in preterm neonates in the immediate postnatal

period because of possible toxicities. A safe and effective dose of lopinavir and ritonavir oral solution in this patient population has

Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations. (5.4, 8.6)

QT interval prolongation and isolated cases of torsade de pointes have been reported although causality could not be established.

Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

PR interval prolongation may occur in some patients. Cases of second and third degree heart block have been reported. Use with

caution in patients with pre-existing conduction system disease, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administering with other drugs that may prolong the PR interval. (5.1, 5.6, 12.3)

Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.7), immune reconstitution syndrome. (5.8),

----ADVERSE REACTIONS---

Commonly reported adverse reactions to lopinavir and ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or

Co-administration of lopinavir and ritonavir can alter the plasma concentrations of other drugs and other drugs may alter the plasma

concentrations of lopinavir. The potential for drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

--- DRUG INTERACTIONS--

--- USE IN SPECIFIC POPULATIONS--

Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)

Total cholesterol and triglycerides elevations. Monitor prior to therapy and periodically thereafter. (5.9)

Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.11)

urticaria, angioedema) or any of its ingredients, including ritonavir. (4)

The following have been observed in patients receiving lopinavir and ritonavir:

not been established. (2.4, 5.2)

redistribution/accumulation of body fat. (5.10)

(5.1. 5.5, 12.3)

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the potential for loss of virologic response and possible resistance and cross resistance. (4)

Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.3)

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use LOPINAVIR AND RITONAVIR TABLETS safely and effectively. See full prescribing information for LOPINAVIR AND RITONAVIR TABLETS. LOPINAVIR and RITONAVIR tablet, for oral use Initial U.S. Approval: 2000

-- RECENT MAJOR CHANGES Contraindications (4) 12/2019 ---INDICATIONS AND USAGE-Lopinavir and ritonavir tablets are HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of

HIV-1 infection in adults and pediatric patients (14 days and older). (1) ---DOSAGE AND ADMINISTRATION-Tablets: May be taken with or without food, swallowed whole and not chewed, broken, or crushed. (2.1) Oral solution: must be taken with food. (2.1)

Total recommended daily dosage is 800/200 mg given once or twice daily.

Lopinavir and ritonavir tablets can be given as once daily or twice daily regimen. See Full Prescribing Information for details.

Lopinavir and ritonavir tablets once daily dosing regimen is not recommended in:
 Adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/l/R/V, K20M/N/R, L24I,

L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V, (12.4) In combination with carbamazepine, phenobarbital, or phenytoin. (7.3)

. In combination with efavirenz, nevirapine, or nelfinavir. (12.3) • In pregnant women. (2.5, 8.1, 12.3)

Pediatric Patients (14 days and older) (2.4): Lopinavir and ritonavir tablets once daily dosing regimen is not recommended in pediatric patients.

Twice daily dose is based on body weight or body surface area. Concomitant Therapy in Adults and Pediatric Patients:

. Dose adjustments of lopinavir and ritonavir tablets may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. Loginavir and ritonavir oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained (2.4, 5.2)

Pregnancy (2.5): • 400/100 mg twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions. There are insufficient data to recommend a lopinavir and ritonavir tablets dose for pregnant patients with any documented lopinavir

and ritonavir tablets-associated resistance substitutions. • No dose adjustment of lopinavir and ritonavir tablets are required for patients during the postpartum period.

----DOSAGE FORMS AND STRENGTHS---

. Tablets: 200 mg lopinavir and 50 mg ritonavir (3) . Tablets: 100 mg lopinavir and 25 mg ritonavir (3)

FULL PRESCRIBING INFORMATION: CONTENTS* INDICATIONS AND USAGE

General Administration Recommendations

2.4 Dosage Recommendations in Pediatric Patients

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Potential for Lopinavir and Ritonavir to Affect Other Drugs

Established and Other Potentially Significant Drug Interactions 7.4 Drugs with No Observed or Predicted Interactions with Lopinavir and Ritonavir

7.2 Potential for Other Drugs to Affect Lopinavir

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

5 WARNINGS AND PRECAUTIONS

5.5 QT Interval Prolongation 5.6 PR Interval Prolongation

5.2 Toxicity in Preterm Neonates

5.7 Diabetes Mellitus/Hyperglycemia

5.8 Immune Reconstitution Syndrome

4 CONTRAINDICATIONS

5.3 Pancreatitis 5.4 Hepatotoxicity

5.9 Lipid Elevations

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

5.10 Fat Redistribution

5.11 Patients with Hemophilia

6.1 Clinical Trials Experience 6.2 Postmarketing Experience

5.12 Resistance/Cross-resistance

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Lactation

8.3 Females and Males of Reproductive Potential 8.4 Pediatric Use

Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

8.5 Geriatric Use 8.6 Hepatic Impairment 10 OVERDOSAGE

11 DESCRIPTION 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action 12.2 Pharmacodynamics

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 Other Studies Supporting Approval in Adult Patients 14.4 Pediatric Studies

16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE

Lopinavir and ritonavir tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 14 days and older

 Genotypic or phenotypic testing and/or treatment history should guide the use of lopinavir and ritonavir tablets. The number
of baseline lopinavir resistance-associated substitutions affects the virologic response to lopinavir and ritonavir tablets [see Microbiology (12.4)]. DOSAGE AND ADMINISTRATION

Lopinavir and ritonavir tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed. Lopinavir and ritonavir oral solution must be taken with food. 2.3 Dosage Recommendations in Adults Lopinavir and ritonavir tablets can be given in once daily or twice daily dosing regimen at dosages noted in Tables 1 and 2. Lopinavir and

ritonavir tablets once daily dosing regimen is not recommended in: Adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24L L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V [see Microbiology (12.4]). In combination with carbamazepine, phenobarbital, or phenytoin [see Drug Interactions (7.3)].

In combination with efavirenz, nevirapine, or nelfinavir [see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]. In pediatric patients younger than 18 years of age [see Dosage and Administration (2.4)].

In pregnant women [see Dosage and Administration (2.5), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)].

Table 1. Recommended Dosage in Adults - Lopinavir and Ritonavir Tablets Once Daily Regimen

Lopinavir and Ritonavir Dosage Form	Recommended Dosage
200 mg/50 mg Tablets	800 mg/200 mg (4 tablets) once daily
80 mg/20 mg per mL Oral Solution	800 mg/200 mg (10 mL) once daily
Table 2. Recommended Dosage in Adults - Lopinavir and Ritona	vir Tablets Twice Daily Regimen
Lopinavir and Ritonavir Dosage Form	Recommended Dosage
200 mg/50 mg Tablets	400 mg/100 mg (2 tablets) twice daily
80 mg/20 mg per mL Oral Solution	400 mg/100 mg (5 mL) twice daily
	administered in combination with efavirenz, nevirapine or nelfinavi

Table 3. Recommended Dosage in Adults - Lopinavir and Ritonavir Tablets Twice Daily Regimen in Combination with Efavirenz,

Novirapino, or Normani	
Lopinavir and Ritonavir Dosage Form	Recommended Dosage
200 mg/50 mg Tablets and 100 mg/25 mg Tablets	500 mg/125 mg (2 tablets of 200 mg/50 mg + 1 tablet of 100 mg/25 mg) twice daily
80 mg/20 mg per mL Oral Solution	520 mg/130 mg (6.5 mL) twice daily
2.4 Dosage Recommendations in Pediatric Patients	

Lopinavir and ritonavir tablets and oral solution are not recommended for once daily dosing in pediatric patients younger than 18 years of age. The dose of the oral solution should be administered using the calibrated cup (supplied) or oral dosing syringe. Lopinavir and ritonavir 100/25 mg tablets should be considered only in children who have reliably demonstrated the ability to swallow the intact tablet. Lopinavir and ritonavir oral solution is not recommended in neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained [see Warnings and Lopinavir and ritonavir oral solution contains ethanol and propylene glycol. Total amounts of ethanol and propylene glycol from all

medicines that are to be given to pediatric patients 14 days to 6 months of age should be taken into account in order to avoid toxicity from these excipients [see Warnings and Precautions (5.2) and Overdosage (10)]. Pediatric Dosage Calculations

Calculate the appropriate dose of lopinavir and ritonavir tablets for each individual pediatric patient based on body weight (kg) or body surface area (BSA) to avoid underdosing or exceeding the recommended adult dose. Body surface area (BSA) can be calculated as follows:

*BSA (m²)= $\sqrt{\frac{\text{Ht (Cm) x Wt (kg)}}{\text{Ht (Cm) x Wt (kg)}}}$

The lopinavir and ritonavir tablet dose can be calculated based on weight or BSA: Based on Weight:

Patient Weight (kg) × Prescribed Iopinavir dose (mg/kg) = Administered Iopinavir dose (mg) Based on BSA:

Patient BSA $(m^2) \times Prescribed lopinavir dose (mg/m^2) = Administered lopinavir dose (mg)$ If lopinavir and ritonavir oral solution is used, the volume (mL) of lopinavir and ritonavir solution can be determined as follows:

Volume of lopinavir and ritonavir solution (mL) = Administered lopinavir dose (mg) ÷ 80 (mg/mL) Oral Solution Dosage Recommendation in Pediatric Patients 14 Days to Less Than 18 Years: Table 4 summarizes the recommended daily dosing regimen for pediatric patients 14 days to less than 18 years of age using the oral

Lopinavir and ritonavir administered in combination with efavirenz, nevirapine, or nelfinavir in patients younger than 6 months of age is

not recommended. Total dose of lopinavir and ritonavir oral solution in pediatric patients should not exceed the recommended adult daily dose of 400/100 mg (5mL) twice daily. Table 4. Lopinavir and Ritonavir Oral Solution Daily Dosage Recommendations in Pediatric Patients 14 days to Less Than 18 Years

Without Concomitant Efavirenz, Nevirapine, or Nelfinavii Based on Weight Based on BSA Frequency Patient Age (mg/kg)

14 days to 6 months	16/4		300/75	Given twice daily	
Older than 6 months to less	Less than15 kg	12/3	230/57.5	Civen turies deily	
than 18 years	15 kg to 40 kg	10/2.5	230/57.5	Given twice daily	
Tablet Dosage Recommendation in	n Pediatric Patients O	lder than 6 M	onths to Less than 18 Years:		
Table 5 provides the dosing recom	mendations for pediat	ric patients o	lder than 6 months to less than 18	years of age based on body weigh	

or body surface area for lopinavir and ritonavir tablets Table 5. Lopinavir and Ritonavir Tablet Daily Dosage Recommendations in Pediatric Patients > 6 Months to < 18 Years of Age

Without Concomitant Efavirenz, Nevirapine, or Nelfinavir						
Body Weight (kg)	Body Surface Area (m²)*	Recommended number of 100/25 mg Tablets Twice Daily				
≥15 to 25	≥0.6 to < 0.9	2				
>25 to 35	≥0.9 to < 1.4	3				
>35	>1 4	4				

Lopinavir and ritonavir oral solution is available for children with a BSA less than 0.6 m² or those who are unable to reliably swallow Concomitant Therapy: Efavirenz, Nevirapine, or Nelfinavir Dosing recommendations using oral solution Table 6 provides the dosing recommendations for pediatric patients older than 6 months to less than 18 years of age based on body

weight or body surface area for lopinavir and ritonavir oral solution when given in combination with efavirenz, nevirapine, or nelfinavir; Table 6. Lopinavir and Ritonavir Oral Solution Daily Dosage Recommendations for Pediatric Patients > 6 Months to < 18 Years of Ang With Concomitant Floring To Matterial Concomitant Floring Control of Matterial Control of Matterial Control of Matterial Control of Matterial Control of Co

Patient Age	Based on \ (mg/k		Based on BSA (mg/m²)	Frequency
> 6 months to	<15 kg	13/3.25	20075	Oirea terias deile
< 18 years	≥15 kg to 45 kg	11/2.75	300/75	Given twice daily

Table 7 provides the dosing recommendations for pediatric patients older than 6 months to less than 18 years of age based on body weight or body surface area for lopinavir and ritonavir tablets when given in combination with efavirenz, nevirapine, or nelfin

Table 7. Lopinavir and Ritonavir Tablet Daily Dosage Recommendations for Pediatric Patients > 6 Months to < 18 Year With Concomitant Efavirenz [†] , Nevirapine, or Nelfinavir [†]					
Body Weight (kg)	Body Surface Area (m²)*	Recommended number of 100/25 mg Tablets Twice Daily			
≥15 to 20	≥0.6 to < 0.8	2			
>20 to 30	≥0.8 to < 1.2	3			
>30 to 45	≥1.2 to <1.7	4			
\A5	>1.7	5 Isee Dosage and Administration (2.4)1			

Please refer to the individual product labels for appropriate dosing in children 2.5 Dosage Recommendations in Pregnancy

Lopinavir and ritonavir oral solution is available for children with a BSA less than 0.6 m² or those who are unable to reliably swallow

Administer 400/100 mg of lopinavir and ritonavir tablets twice daily in pregnant patients with no documented lopinavir-associated Once daily lopinavir and ritonavir tablet dosing is not recommended in pregnancy [see Use in Specific Populations (8.1) and Clinical

There are insufficient data to recommend dosing in pregnant women with any documented lopinavir-associated resistance

No dosage adjustment of lopinavir and ritonavir tablets are required for patients during the postpartum period Avoid use of lopinavir and ritonavir oral solution in pregnant women [see Use in Specific Populations (8.1)].

3 DOSAGE FORMS AND STRENGTHS Lopinavir and Ritonavir Tablets USP, containing 200 mg lopinavir and 50 mg ritonavir are light yellow film-coated ovaloid tablets

. Lopinavir and Ritonavir Tablets USP, containing 100 mg lopinavir and 25 mg ritonavir are light yellow film-coated capsule shaped

tablets debossed with 'D91' on one side and plain on other side. 4 CONTRAINDICATIONS Lopinavir and ritonavir tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urticaria, angioedema) to any of its ingredients, Lopinavir and ritonavir tablets are contraindicated with drugs that are highly dependent on CYP3A for clearance and for which

Clinical Pharmacology (12.3)]. Alpha 1- Adrenoreceptor Antagonist : alfuzosin

elevated plasma concentrations are associated with serious and/or life-threatening reactions [see Drug Interactions (7.1) and Antianginal: ranolazine Antiarrhythmic: dronedarone Anti-gout: colchicine

Antipsychotics: lurasidone, pimozide Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine GI Motility Agent: cisapride Hepatitis C direct acting antiviral: elbasvir/grazoprevi

HMG-CoA Reductase Inhibitors: Iovastatin, simvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: Iomitapide

PDE5 Inhibitor: sildenafil (Revatio®) when used for the treatment of pulmonary arterial hypertension Sedative/Hypnotics: triazolam, orally administered midazolam

Lopinavir and ritonavir tablets are contraindicated with drugs that are potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and crossesistance [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]. Anticancer Agents: apalutamide

Antimycobacterial: rifampin Herbal Products: St. John's Wort (hypericum perforatum) WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of Iopinavir and ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving lopinavir and ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of lopinavir and ritonavir, respectively. These interactions may lead to: · Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of

Clinically significant adverse reactions from greater exposures of lopinavir and ritonavir. Loss of therapeutic effect of lopinavir and ritonavir and possible development of resistance.

See Table 12 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations [see Drug Interactions (7)]. Consider the potential for drug interactions prior to and during lopinavir and ritonavir therapy; review concomitant medications during lopinavir and ritonavir therapy, and monitor for the adverse reactions associated with the concomitant medications [see Contraindications (4) and Drug Interactions (7)].

5.2 Toxicity in Preterm Neonates Lopinavir and ritonavir oral solution contains the excipients ethanol and propylene glycol. When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm

neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol. thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to

death have been reported, predominantly in preterm neonates receiving lopinavir and ritonavir oral solution Lopinavir and ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of lopinavir and ritonavir oral solution in this patient population has not been established. However, if the benefit of using lopinavir and ritonavir oral solution to treat HIV infection in infants immediately after birth outweighs the potentia risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to lopinavir and ritonavir oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of ethanol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients [see Dosage and Administration (2.4) and Overdosage (10)].

5.3 Pancreatitis elevations. In some cases, fatalities have been observed. Although a causal relationship to lopinavir and ritonavir has not been established, marked triglyceride elevations are a risk factor for development of pancreatitis [see Warnings and Precautions (5.9)]. Patients with advanced HIV-1 disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during lopinavir and ritonavir therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and lopinavir and ritonavir and/or other antiretroviral therapy should be suspended as clinically appropriate

Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of lopinavir and ritonavir. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with lopinavir and ritonavir therapy has not been established.

early as 7 days after the initiation of lopinavir and ritonavir in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with lopinavir and ritonavir therapy has not been established. Appropriate laboratory testing should be conducted prior to initiating therapy with lopinavir and ritonavir and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be considered in the patients with underlying chronic hepatitis or cirrhosis, especially during the first several months of lopinavir and ritonavir treatment [see Use in Specific Populations (8.6)]. 5.5 QT Interval Prolongation

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as

Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of lopinavir and ritonavir could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval [see Clinical Pharmacology (12.3)]. 5.6 PR Interval Prolongation

Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. Lopinavir and ritonavir should be used with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities The impact on the PR interval of co-administration of lopinavir and ritonavir with other drugs that prolong the PR interval (including

calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of lopinavir and ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended [see Clinical Pharmacology (12.3)]. 5.7 Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 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 practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consider monitoring for hyperglycemia, new onset diabetes mellitus or an exacerbation of diabetes

mellitus in patients treated with lopinavir and ritonavir 5.8 Immune Reconstitution Syndrome Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lopinavir and ritonavir. 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 jirovecii pneumonia [PCP], 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. 5.9 Lipid Elevations Treatment with lopinavir and ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides [see Adverse Reactions (6.1). Triglyceride and cholesterol testing should be performed prior to initiating lopinavir and ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-

drug interactions with lopinavir and ritonavir and HMG-CoA reductase inhibitors [see Contraindications (4) and Drug Interactions (7.3)]. 5.10 Fat Redistribution Redistribution/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. 5.11 Patients with Hemophilia

Increased bleeding, including spontaneous skin hematomas and hemarthrosis have been reported 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, trea with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.12 Resistance/Cross-resistance Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in lopinavir and ritonavir-treated patients, it is unknown what effect therapy with lopinavir and ritonavir will have on the activity of subsequently administered protease

inhibitors [see Microbiology (12.4)]. 6 ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling.

QT Interval Prolongation, PR Interval Prolongation [see Warnings and Precautions (5.5, 5.6)]
 Drug Interactions [see Warnings and Precautions (5.1)]

Pancreatitis [see Warnings and Precautions (5.3)] Hepatotoxicity [see Warnings and Precautions (5.4)] 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 clinical practice. Adverse Reactions in Adults The safety of lopinavir and ritonavir has been investigated in about 2,600 patients in Phase II-IV clinical trials, of which about 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some

studies, lopinavir and ritonavir was used in combination with efavirenz or nevirapine. In clinical studies the incidence of diarrhea in patients treated with either lopinavir and ritonavir capsules or tablets was greater in those

patients treated once daily than in those patients treated twice daily. Any grade of diarrhea was reported by at least half of patients taking once daily lopinavir and ritonavir capsules or tablets. At the time of treatment discontinuation, 4.2 to 6.3% of patients taking once daily lopinavir and ritonavir and 1.8 to 3.7% of those taking twice daily lopinavir and ritonavir reported ongoing diarrhea. Commonly reported adverse reactions to lopinavir and ritonavir included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and

hypercholesterolemia may occur later. The following have been identified as adverse reactions of moderate or severe intensity (Table 8):

Table 8. Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving Lopinavir and

System Organ Class (SOC) and Adverse Reaction BLOOD AND LYMPHATIC SYSTEM DISORDERS 2.1 leukopenia and neutropenia* 44 1.7 1.3 CARDIAC DISORDERS 0.4 atherosclerosis such as myocardial infarction* rioventricular block* 0.1 0.1 EAR AND LABYRINTH DISORDERS 0.3 innitus 0.2 **ENDOCRINE DISORDERS** 0.81 16 EYE DISORDERS 0.3 visual impairment **GASTROINTESTINAL DISORDERS** 510 19.5 diarrhea 269 10.3

vomiting*	177	6.8
abdominal pain (upper and lower)*	160	6.1
gastroenteritis and colitis*	66	2.5
dyspepsia	53	2.0
pancreatitis*	45	1.7
Gastroesophageal Reflux Disease (GERD)*	40	1.5
hemorrhoids	39	1.5
flatulence	36	1.4
abdominal distension	34	1.3
constipation*	26	1.0
stomatitis and oral ulcers*	24	0.9
duodenitis and gastritis*	20	0.8
gastrointestinal hemorrhage including rectal hemorrhage*	13	0.5
dry mouth	9	0.3
gastrointestinal ulcer*	6	0.2
fecal incontinence	5	0.2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION	DNS	
fatigue including asthenia*	198	7.6
HEPATOBILIARY DISORDERS		
hepatitis including AST, ALT, and GGT increases*	91	3.5
hepatomegaly	5	0.2
cholangitis	3	0.1
hepatic steatosis	3	0.1
IMMUNE SYSTEM DISORDERS		
hypersensitivity including urticaria and angioedema*	70	2.7
immune reconstitution syndrome	3	0.1
INFECTIONS AND INFESTATIONS		
upper respiratory tract infection*	363	13.9
lower respiratory tract infection*	202	7.7
skin infections including cellulitis, folliculitis, and furuncle*	86	3.3
METABOLISM AND NUTRITION DISORDERS		
hypercholesterolemia*	192	7.4
hypertriglyceridemia*	161	6.2
weight decreased*	61	2.3
decreased appetite	1	2.0
blood glucose disorders including diabetes mellitus*	52	2.0
	52 30	1.1
weight increased*	-	
weight increased* lactic acidosis*	30	1.1
	30 20	1.1

usculoskeletal pain including arthralgia and back pain

System Organ Class (SOC) and Adverse Reaction	n	%
muscle disorders such as weakness and spasms*	34	1.3
rhabdomyolysis*	18	0.7
osteonecrosis	3	0.1
NERVOUS SYSTEM DISORDERS		
neadache including migraine*	165	6.3
nsomnia*	99	3.8
neuropathy and peripheral neuropathy*	51	2.0
dizziness*	45	1.7
ngeusia*	19	0.7
convulsion*	9	0.3
remor*	9	0.3
cerebral vascular event*	6	0.2
PSYCHIATRIC DISORDERS		
nxiety*	101	3.9
ibnormal dreams*	19	0.7
ibido decreased	19	0.7
RENAL AND URINARY DISORDERS		
enal failure*	31	1.2
nematuria*	20	0.8
nephritis*	3	0.1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
erectile dysfunction*	34	1.71
nenstrual disorders - amenorrhea, menorrhagia*	10	1.72
KIN AND SUBCUTANEOUS TISSUE DISORDERS		
ash including maculopapular rash*	99	3.8
podystrophy acquired including facial wasting*	58	2.2
lermatitis/rash including eczema and seborrheic dermatitis*	50	1.9
iight sweats*	42	1.6
oruritus*	29	1.1
lopecia	10	0.4
capillaritis and vasculitis*	3	0.1
ASCULAR DISORDERS		
ypertension*	47	1.8
leep vein thrombosis*	17	0.7
Represents a medical concept including several similar MedDRA PT Percentage of male population (N=2,038) Percentage of female population (N=574)	s	
aboratory Abnormalities in Adults		

The percentages of adult patients treated with combination therapy with Grade 3 to 4 laboratory abnormalities are presented in Table 9 (treatment-naïve patients) and Table 10 (treatment-experienced patients).

2 Criterion for Study 730 was >5x ULN (AST/ALT).

			y 863 /eeks)	Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit ¹	Lopinavir and Ritonavir 400/100 mg Twice Daily + d4T +3TC (N = 326)	Nelfinavir 750 mg Three Times Daily + d4T + 3TC (N = 327)	Lopinavir and Ritonavir Twice Daily + d4T + 3TC (N = 100)	Lopinavir and Ritonavir Once Daily + TDF +FTC (N=333)	Lopinavir and Ritonavir Twice Daily + TDF +FTC (N=331)
Chemistry	High					
Glucose	> 250 mg/dL	2%	2%	4%	0%	<1%
Uric Acid	> 12 mg/dL	2%	2%	5%	<1%	1%
SGOT/ AST ²	> 180 U/L	2%	4%	10%	1%	2%
SGPT/ ALT ²	>215 U/L	4%	4%	11%	1%	1%
GGT	>300 U/L	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	4%	N/A	N/A
Lipase	>2 x ULN	N/A	N/A	N/A	3%	5%
Chemistry	Low					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	2%	2%
Hematology	Low					
Neutrophils	<0.75 x 10 ⁹ /L	1%	3%	5%	2%	1%

Table 10. Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 Weeks)		Study 957 ² and Study 765 ³ (84-144 Weeks)	Study 802 (48 Weeks)	
Variable	Limit ¹	Lopinavir and Ritonavir 400/100 mg Twice Daily + NVP + NRTIS (N = 148)	Investigator- Selected Protease Inhibitor(s) + NVP + NRTIS (N = 140)	Lopinavir and Ritonavir Twice Daily + NNRTI + NRTIs (N = 127)	Lopinavir and Ritonavir 800/200 mg Once Daily +NRTIs (N=300)	Lopinavir and Ritonavir 400/100 mg Twice Daily +NRTIs (N=299)
Chemistry	High					
Glucose	>250 mg/dL	1%	2%	5%	2%	2%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%	1%	1%
SGOT/AST ⁴	>180 U/L	5%	11%	8%	3%	2%
SGPT/ALT ⁴	>215 U/L	6%	13%	10%	2%	2%
GGT	>300 U/L	N/A	N/A	29%	N/A	N/A
Total Cholesterol	>300 mg/dL	20%	21%	39%	6%	7%
Triglycerides	>750 mg/dL	25%	21%	36%	5%	6%
Amylase	>2 x ULN	4%	8%	8%	4%	4%
Lipase	>2 x ULN	N/A	N/A	N/A	4%	1%
Creatine Phosphokinase	>4 x ULN	N/A	N/A	N/A	4%	5%
Chemistry	Low					
Calculated Creatinine Clearance	<50 mL/min	N/A	N/A	N/A	3%	3%
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%	1%	<1%
Hematology	Low					
Neutrophils	<0.75 x 10 ⁹ /L	1%	2%	4%	3%	4%
Hemoglobin	<80 g/L	1%	1%	1%	1%	2%

weeks. Patients received lopinavir and ritonavir in combination with NRTIs and efavirenz. 3 Includes clinical laboratory data from patients receiving 400/100 mg twice daily (n = 36) or 400/200 mg twice daily (n = 34) for 144 reeks. Patients received lopinavir and ritonavir in combination with NRTIs and nevirapine. 4 Criterion for Study 802 was >5x ULN (AST/ALT). Adverse Reactions in Pediatric Patients

navir and ritonavir oral solution dosed up to 300/75 mg/m² has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse reaction profile seen during Study 940 was similar to that for adult patients. Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity reported in pediatric patients treated with combination therapy for up to 48 weeks in Study 940. A total of 8 patients experienced adverse reactions of moderate to severe intensity. The adverse reactions meeting these criteria and reported for the 8 subjects include: hypersensitivity (characterized by fever, rash and jaundice), pyrexia, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, alanine aminotransferase increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (N = 3).

Lopinavir and ritonavir oral solution dosed at 300/75 mg/m² has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe inter nsity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2). Lopinavir and ritonavir oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/m²

(without concomitant NNRTI) and 480/120 mg/m² (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities. Laboratory Abnormalities in Pediatric Patients

The percentages of pediatric patients treated with combination therapy including lopinavir and ritonavir with Grade 3 to 4 laboratory abnormalities are presented in Table 11. Table 11. Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients in Study 940

Variable	Limit ¹	Lopinavir and Ritonavir Twice Daily + RTIs (N = 100)
Chemistry	High	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SG0T/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7%2
Chemistry	Low	
Sodium	< 130 mEq/L	3%
Hematology	Low	
Platelet Count	< 50 x 10 ⁹ /L	4%
Neutrophils	< 0.40 x 10 ⁹ /L	2%

6.2 Postmarketing Experience The following adverse reactions have been reported during postmarketing use of lopinavir and ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to lopinavir and ritonavir exposure. Body as a Whole

Redistribution/accumulation of body fat has been reported [see Warnings and Precautions (5.10)]. Bradyarrhythmias. First-degree AV block, second-degree AV block, third-degree AV block, QTc interval prolongation, torsades (torsade) de

Skin and Appendages $\label{thm:constraints} \mbox{Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and erythema multiforme.}$ 7 DRUG INTERACTIONS 7.1 Potential for Lopinavir and Ritonavir to Affect Other Drugs

Published data suggest that lopinavir is an inhibitor of OATP1B1.

pointes [see Warnings and Precautions (5.5, 5.6)].

Lopinavir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with lopinavir and ritonavir. Thus, co-administration of lopinavir and ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 12. Additionally, lopinavir and ritonavir induces glucuronidation

These examples are a quide and not considered a comprehensive list of all possible drugs that may interact with lopinavir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information 7.2 Potential for Other Drugs to Affect Lopinavir

Lopinavir/ritonavir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce lopinavir and ritonavir's therapeutic effect. Although not observed in the lopinavir and ritonavir/ketoconazole drug interaction study, co-administration of lopinavir and ritonavir and ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations. 7.3 Established and Other Potentially Significant Drug Int Table 12 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be

led based on drug interaction studies or predicted interaction [see Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)] for magnitude of interaction.

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comments
	1	HIV-1 Antiviral Agents
HIV-1 Protease Inhibitor: fosamprenavir/ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co- administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir*	↑indinavir	Decrease indinavir dose to 600 mg twice daily, when co-administered with lopinavir and ritonavir 400/ 100 mg twice daily. Lopinavir and ritonavir once daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir*	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	Lopinavir and ritonavir once daily in combination with nelfinavir is not recommended [see Dosage and Administration (2)].
HIV-1 Protease Inhibitor: ritonavir*	↑ lopinavir	Appropriate doses of additional ritonavir in combination with lopinavir and ritonavir with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: saquinavir	↑ saquinavir	The saquinavir dose is 1000 mg twice daily, when co-administered with lopinavir and ritonavir 400/100 mg twice daily. Lopinavir and ritonavir once daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir*	↓ lopinavir	Co-administration with tipranavir (500 mg twice daily) and ritonavir (200 mg twice daily) is not recommended.
HIV CCR5 – Antagonist: maraviroc*	↑ maraviroc	When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for maraviroc.
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ lopinavir	Increase the dose of lopinavir and ritonavir tablets to 500/125 mg when lopinavir and ritonavir tablet is co-administered with efavirenz or nevirapine. Lopinavir and ritonavir once daily in combination with efavirenz or nevirapine is not recommended [see Dosage and Administration (2)].
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor:		Lopinavir and ritonavir tablets can be administered simultaneously with didanosine without food.
didanosine		For lopinavir and ritonavir oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after lopinavir and ritonavir oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir disoproxil fumarate*	↑ tenofovir	Patients receiving lopinavir and ritonavir and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitors: abacavir zidovudine	↓ abacavir ↓ zidovudine	The clinical significance of this potential interaction is unknown.
	•	Other Agents
Alpha 1- Adrenoreceptor	↑ alfuzosin	Contraindicated due to potential hypotension [see Contraindications (4)].

Drug Name	Lopinavir or Concomitant Drug	
Antianginal: ranolazine Antiarrhythmics:	↑ ranolazine ↑ dronedarone	Contraindicated due to potential for serious and/or life-threatening reactions [see Contraindications (4)]. Contraindicated due to potential for cardiac arrhythmias [see Contraindications
dronedarone Antiarrhythmics e.g.	↑ antiarrhythmics	(4)]. Caution is warranted and therapeutic concentration monitoring (if available)
amiodarone, bepridil, lidocaine (systemic),		is recommended for antiarrhythmics when co-administered with lopinavir and ritonavir.
quinidine Anticancer Agents:	↑ anticancer agents	Apalutamide is contraindicated due to potential for loss of virologic response
abemaciclib, apalutamide, encorafenib,	↓ lopinavir/ritonavir#	and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Avoid co-administration of encoratenib or ivosidenib with lopinavir and
ibrutinib ivosidenib, dasatinib,		Avoid co-administration of encorafenib or ivosidenib with lopinavir and ritonavir due to potential risk of serious adverse events such as QT interval prolongation. If co-administration of encorafenib with lopinavir and ritonavir cannot be avoided modify dose as recommended in encorafenib LISPI If co-
neratinib, nilotinib,		cannot be avoided, modify dose as recommended in encorafenib USPI. If co- administration of ivosidenib with lopinavir and ritonavir cannot be avoided, reduce ivosidenib dose to 250 mg once daily.
venetoclax, vinblastine, vincristine		Avoid use of neratinib, venetoclax or ibrutinib with lopinavir and ritonavir. For vincristine and vinblastine, consideration should be given to temporarily
		withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when lopinavir and ritonavir is administered concurrently with vincristine or vinblastine. If the
		antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A
		or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with
		and dasadilin may be necessary for patients requiring to varialinisation with strong CYP3A inhibitors such as lopinavir and ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulants: warfarin,	↑↓ warfarin	Concentrations of warfarin may be affected. Initial frequent monitoring of the INR during lopinavir and ritonavir and warfarin co-administration is
rivaroxaban	↑ rivaroxaban	recommended. Avoid concomitant use of rivaroxaban and lopinavir and ritonavir. Co- administration of lopinavir and ritonavir and rivaroxaban may lead to increased
Anticonvulsants:	↓ lopinavir	risk of bleeding. Lopinavir and ritonavir may be less effective due to decreased lopinavir
carbamazepine, phenobarbital, phenytoin	↓ phenytoin	plasma concentrations in patients taking these agents concomitantly and should be used with caution. Lopinavir and ritonavir once daily in combination with carbamazepine, phenobarbital, or phenytoin is not recommended. In
p		addition, co-administration of phenytoin and lopinavir and ritonavir may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should
Anticonvulsants: lamotrigine,	↓ lamotrigine ↓ or ↔ valproate	be monitored when co-administering with lopinavir and ritonavir A dose increase of lamotrigine or valproate may be needed when co- administered with lopinavir and ritonavir and therapeutic concentration
valproate	V OI C Varpioato	monitoring for lamotrigine may be indicated; particularly during dosage adjustments.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Patients receiving lopinavir and ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose
Anti-infective:	↑ clarithromycin	of trazodone should be considered. For patients with renal impairment, adjust clarithromycin dose as follows:
clarithromycin		 For patients on lopinavir and ritonavir with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients on lopinavir and ritonavir with CL_{CR} < 30 mL/min the dose of
		clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole,	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. The coadministration of voriconazole and lopinavir and ritonavir should be
voriconazole isavuconazonium	↑ isavuconazonium	avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Isavuconazonium and lopinavir and ritonavir should
sulfate* Anti-gout:	↑ colchicine	be coadministered with caution. Alternative antifungal therapies should be considered in these patients. Contraindicated due to potential for serious and/or life-threatening reactions
colchicine	T COICHICHE	in patients with renal and/or hepatic impairment [see Contraindications (4)]. For patients with normal renal or hepatic function:
		Treatment of gout flares-co-administration of colchicine in patients on lopinavir and ritonavir: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose
		to be repeated no earlier than 3 days. Prophylaxis of gout flares-co-administration of colchicine in patients on
		lopinavir and ritonavir: If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.
		If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.
		Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on lopinavir and ritonavir: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifampin	↓ lopinavir	Contraindicated due to potential loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors or
Antimycobacterial:	↑ bedaquiline	other co-administered antiretroviral agents [see Contraindications (4)]. Bedaquiline should only be used with lopinavir and ritonavir if the benefit of
bedaquiline Antimycobacterial:	↑ rifabutin and	co-administration outweighs the risk. Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/
rifabutin*	rifabutin metabolite	day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted in patients receiving the completion. Further descendent to the completion of the completion of the completion.
Antiparasitic: atovaquone	↓ atovaquone	the combination. Further dosage reduction of rifabutin may be necessary. Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics:	↑ lurasidone	De needed. Contraindicated due to potential for serious and/or life-threatening reactions see Contraindications (4)].
pimozide	↑ pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias <i>[see Contraindications (4)]</i> .
Antipsychotics: quetiapine	↑ quetiapine	Initiation of lopinavir and ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine
		exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on
		adverse reaction monitoring. Initiation of quetiapine in patients taking lopinavir and ritonavir:
		Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Contraceptive: ethinyl estradiol*	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when lopinavir and ritonavir is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are
Dihydropyridine Calcium	↑ dihydropyridine	recommended. Clinical monitoring of patients is recommended and a dose reduction of the
Channel Blockers: e.g. felodipine, nifedipine,	calcium channel blockers	dihydropyridine calcium channel blocker may be considered.
nicardipine Disulfiram/metronidazole		Lopinavir and ritonavir oral solution contains ethanol, which can produce
		disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Endothelin Receptor Antagonists: bosentan	↑ bosentan	Co-administration of bosentan in patients on lopinavir and ritonavir: In patients who have been receiving lopinavir and ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual
555511411		tolerability. Co-administration of lopinavir and ritonavir in patients on bosentan:
		Discontinue use of bosentan at least 36 hours prior to initiation of lopinavir and ritonavir. After at least 10 days following the initiation of lopinavir and ritonavir, resume
		bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot Derivatives: dihydroergotamine, ergotamine,	↑ ergot derivatives	Contraindicated due to potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues [see Contraindications (4)].
methylergonovine GI Motility Agent: cisapride	↑ cisapride	Contraindicated due to potential for cardiac arrhythmias [see Contraindications
	· oleaphiae	(4)].
GnRH Receptor	↑ elagolix	Concomitant use of elagolix 200 mg twice daily and lopinavir and ritonavir for
	↑ elagolix ↓ lopinavir/ritonavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting		more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations
GnRH Receptor Antagonists: elagolix	↓ lopinavir/ritonavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir*	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)].
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ pibrentasvir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ pibrentasvir ↑ simeprevir ↑ sofosbuvir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ pibrentasvir ↑ simeprevir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ pibrentasvir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir/voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir*	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ velpatasvir ↑ vomitasvir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir/voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir ↑ lovastatin	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: sboceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors:	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)].
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: Iovastatin simvastatin	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ ritonavir ↑ paritaprevir ↑ ritonavir ↓ lopinavir ↓ lopinavir	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see
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GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin dicrosomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus,	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ woxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin dicrosomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ velpatasvir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above)	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: sboceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta- adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone,*	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↔ dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindications (4)]. Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increase grosure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation,
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin dicrosomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics:	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ↑ ritonavir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ simvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolis 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose; do not exceed rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir.
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin forsuvastatin microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl	↓ lopinavir/ritonavir ↑ lopinavir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ velpatasvir ↑ rotolaprevir ↑ ritonavir ↑ paritaprevir ↑ ritonavir ↑ ritonavir ↑ dasabuvir ↓ lopinavir ↑ lowastatin ↑ samvastatin ↑ arovastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolis 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Sildenafil when used for the treatment of pulmonary arterial hypertension
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin forsuvastatin microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avanafil, suldenafil, tadalafil,	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ rosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolis 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose; do not exceed rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of soficial. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tack/cycardia. Dosage of methadone may need to be increased when co-administered with lopinavir
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GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta- adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ voxilaprevir ↑ orobitasvir ↑ orobitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ simvastatin ↑ tosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ sidanafil ↑ tadalafil ↑ tadalafil ↑ tadalafil ↑ avanafil ↑ tadalafil ↑ tadalafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Careful monitoring of therapeutic and adverse effects (including potentially datal respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir and ritonavir. Sildenafil when used for the treatment of pulmonary arterial hypertension (Revation ⁹) is contraindicated due to the potential for sildenafil-associated adverse events, including visual abnormalities,
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin forsuvastatin microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avanafil, suldenafil, tadalafil,	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ voxilaprevir ↑ orobitasvir ↑ orobitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ simvastatin ↑ tosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ sidanafil ↑ tadalafil ↑ tadalafil ↑ tadalafil ↑ avanafil ↑ tadalafil ↑ tadalafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir and ritonavir with avan
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GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin forsuvastatin microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrollimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avanafil, suldenafil, tadalafil,	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ simeprevir ↑ sofosbuvir ↑ voxilaprevir ↑ orobitasvir ↑ orobitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ lopinavir ↑ lovastatin ↑ simvastatin ↑ simvastatin ↑ tosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ sidanafil ↑ tadalafil ↑ tadalafil ↑ tadalafil ↑ avanafil ↑ tadalafil ↑ tadalafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/partiaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin 10 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increase storang CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Gareful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with lopinavir and ritonavir with these drugs may result in an increase in PDE5 inhibitor associated adverse react
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GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ velpatasvir ↑ romitasvir ↑ paritaprevir ↑ ritonavir ↑ dasabuvir ↓ lopinavir ↑ lowastatin ↑ samustatin ↑ torstamatinib ↑ rosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib methadone ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ avanafil ↑ triazolam ↑ triazolam	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elvations. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose, do not exceed rosuvastatin obse carefully and use the lowest necessary dose, do not exceed rosuvastatin to mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 mibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitagide is contraindicated due to potential for hepatotoxicity [see Contraindications (4)]. Therapeutic concentration monitoring is recommended of to rimmunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with sameterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administratio
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, fentanyl PDE5 inhibitors: avanafil, svandanii, tadalafil, vardenafil vardenafil	↓ Iopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ Iopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ Iopinavir ↑ Iovastatin ↑ simvastatin ↑ simvastatin ↑ tosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ avanafil ↑ tavanafil ↑ tavanafil ↑ vardenafil ↑ vardenafil ↑ vardenafil ↑ vardenafil	nore than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase levalions. Limit conormitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevii/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atonvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose, do not exceed rosuvastatin in Img/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lippinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatnib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT protinogation, palpitations and sinus tachycardia. Do not use lopinavir and ritonavir with baranetic including potentially fatal respiratory depression) is recommended when rentanyl is concomitantly administered with lopinavir and ritonavir with avanafti posage of methadone may need to be increased when prescribing sildenafti. radalafti, or varde
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir/ ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, fentanyl PDE5 inhibitors: avanafil, saladafali, vardenafil vardenafil	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ velpatasvir ↑ romitasvir ↑ paritaprevir ↑ ritonavir ↑ dasabuvir ↓ lopinavir ↑ lowastatin ↑ samustatin ↑ torstamatinib ↑ rosuvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib methadone ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ triazolam ↑ triazolam	nore than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elvations. Limit conormitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvir/velpatasvir/voxilaprevir, or ombitasvir/paritaprevii/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin in 0 mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide is contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatnib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events, associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Do not use lopinavir and ritonavir with avanafti persecular and ritonavir is not recommended. The combination may result in increased with portionary and prolonged erection, and spinavir and ritonavir with b
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: footamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avandfil, siddenafil, tadalafil, vardenafil	↓ Iopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ Iopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ mitavir ↑ paritaprevir ↑ ritonavir ↑ Iopinavir ↑ Iowastatin ↑ arovastatin ↑ arovastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↓ wardenafil ↑ tavanafil ↑ vardenafil	nore than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase levalinos. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosburir/velpatasvir/voxilaprevir, or ombitasvir/paritapreviir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin lor mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when fentanyl is concomitantly adverse events. Including visual ahommalities, lipyotension, prolonged erection, an
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. c.yclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, fentanyl PDE5 inhibitors: avanafil, suldalafil, vardenafil vardenafil vardenafil	↓ lopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ lopinavir ↓ boceprevir ↓ ridoxir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ombitasvir ↑ paritaprevir ↑ ritonavir ← dasabuvir ↓ lopinavir ↑ lowastatin ↑ samustatin ↑ satorvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↑ avanafil ↑ tadalafil ↑ tadalafil ↑ vardenafil ↑ vardenafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transminase elevations. Limit concomitant use of leagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosbuvrir/elpatasvir/voxilaprevir, or ombitasvir/paritaprevir/ritonavir and dasabuvr. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin for myday. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase general proximacy 27-fold. Concominat use of moderate or strong CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increase the exposure of lomitapide, with strong inhibitors increase general proximacy 27-fold. Concominative of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity [see Contraindicators (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events. Including visual abmernalities, hypothension, projection, palpitations and sinuis tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Sidenafil (Revatore) is contraindicated due to the potential for sidenafil-ass
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin frosuvastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. c.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, fentanyl PDE5 inhibitors: avanafil, sundafafil, vardenafil vardenafil vardenafil vardenafil	↓ Iopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ Iopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ mitavir ↑ paritaprevir ↑ ritonavir ↑ Iopinavir ↑ Iowastatin ↑ arovastatin ↑ arovastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↓ wardenafil ↑ tavanafil ↑ vardenafil	nore than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase levalinos. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindicated due to increased risk of alanine transaminase (ALT) elevations [see Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/pibrentasvir, simeprevir, sofosburir/velpatasvir/voxilaprevir, or ombitasvir/paritapreviir/ritonavir and dasabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors [see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin lor mg/day. Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximationations (4). Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when fentanyl is concomitantly adverse events. Including visual ahommalities, lipyotension, prolonged erection, an
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: salmeterol Narcotic Analgesics: methadone, * fentanyl PDE5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil devanuel sone fluticasone ducksomethasone fluticasone ducksomethasone fluticasone ducksomethasone fluticasone	↓ Iopinavir/ritonavir ↑ elbasvir/grazoprevir ↓ Iopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ mitavir ↑ paritaprevir ↑ ritonavir ↑ Iopinavir ↑ Iowastatin ↑ arovastatin ↑ arovastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↓ wardenafil ↑ tavanafil ↑ vardenafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transmisase elevations. Limit concomitant use of elegabit, 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/plbrentaxvir, simegrevir, sofosbuvrir-leplatasvir/voxilaprevir, or ombitasvir/partiaprevir/ritonavir and disabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors /see Contraindications (4)]. Contraindicated due to potential for myopathy including rhabdomyolysis /see Contraindications (4)]. Los atorvastatin with caution and at the lowest necessary dose, do not exceed rossvastatin 10 mg/day. Los atorvastatin with caution and at the lowest necessary dose, on the exceed rossvastatin of ose carefully and use the lowest necessary dose; do not exceed rossvastatin of see a sensitive substants for CVP3A4 metabolism. CVP3A4 inhibitors increase the exposure of iomitapide, with strong inhibitors of service of the sepaper of iomitapide and the contraindication of self-protection of the potential for hepatotoxicity /see Contraindications (4)]. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with lopinavir and ritonavir. Monitor for toxicities of R406 such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including OT prolongation, palpitations and sinus tachycardia. Dosage of methadone may need to be increased when co-administered with lopinavir and ritonavir. Fostamatinib dose reduction may be required. Concurrent administration of salmeterol and lopinavir and ritonavir is not recommended. The combina
GnRH Receptor Antagonists: elagolix Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antiviral: elbasvir/ grazoprevir Hepatitis C direct acting antivirals: boceprevir* glecaprevir/pibrentasvir simeprevir sofosbuvir/velpatasvir /voxilaprevir ombitasvir/paritaprevir/ ritonavir and dasabuvir* Herbal Products: St. John's Wort (hypericum perforatum) Lipid-modifying agents HMG-CoA Reductase Inhibitors: lovastatin simvastatin atorvastatin rosuvastatin fosuvastatin Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide Immunosuppressants: e.g. c.yclosporine, tacrolimus, sirolimus Kinase Inhibitors: fostamatinib (also see anticancer agents above) Long-acting beta-adrenoceptor Agonist: Salmeterol Narcotic Analgesics: methadone,* fentanyl PDE5 inhibitors: avandarii, saldalafii, vardenafiil vardenafiil vardenafiil	↓ Iopinavir/ritonavir ↑ elbasvir/grazoprevir ↑ Iopinavir ↓ boceprevir ↓ ritonavir ↑ glecaprevir ↑ sofosbuvir ↑ velpatasvir ↑ voxilaprevir ↑ ritonavir ↑ paritaprevir ↑ ritonavir ↑ Iopinavir ↑ Iowastatin ↑ atorvastatin ↑ atorvastatin ↑ lomitapide ↑ immunosuppressants ↑ fostamatinib metabolite R406 ↑ salmeterol ↓ methadone ↑ fentanyl ↓ upinavir ↑ avanafil ↑ sidenafil ↑ tadalafil ↑ vardenafil ↑ vardenafil	more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transminase elevation. Limit concomitant use of elagolix 150 mg once daily and lopinavir and ritonavir to 6 months. Contraindications (4)]. It is not recommended to co-administer lopinavir and ritonavir and boceprevir, glecaprevir/plorentasvir, simeprevir, sofosbuvriv-lepistasvir/voxilsprevir, or ombitasvir/partiaprevir/ritonavir and disabuvir. Contraindicated due to potential for loss of virologic response and possible resistance to lopinavir and ritonavir or to the class of protease inhibitors /see Contraindications (4)]. Use atorvastatin with caution and at the lowest necessary dose, do not exceed rosuvastatin dose carefully and use the lowest necessary dose, on the consumption of the protection of t

7.4 Drugs with No Observed or Predicted Interactions with Lopinavir and Ritonavir Drug interaction or clinical studies reveal no clinically significant interaction between lopinavir and ritonavir and desigramine (CYP2D6 probe), etravirine, pitavastatin, pravastatin, stavudine, lamivudine, omeprazole, raltegravir, ranitidine, or rilpivirine. Based on known metabolic profiles, clinically significant drug interactions are not expected between lopinavir and ritonavir and dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole. 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

refers to interaction with analutamid

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lopinavir and ritonavir during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263. Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see Data). The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15 to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation (see Data). No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits; however embryonic and fetal developmental toxicities occurred in rats administered maternally toxic doses. Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period Administer 400/100 mg of lopinavir and ritonavir twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]. There are insufficient data to recommend lopinavir and ritonavir dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. No dose adjustment of lopinavir and ritonavir is required for patients during the postpartum period.

Once daily lopinavir and ritonavir dosing is not recommended in pregnancy Avoid use of lopinavir and ritonavir oral solution during pregnancy due to the ethanol content. Lopinavir and ritonavir oral solution contains the excipients ethanol and propylene glycol.

Lopinavir and ritonavir was evaluated in 12 HIV-infected pregnant women in an open-label pharmacokinetic trial [see Clinical Pharmacology (12.3)]. No new trends in the safety profile were identified in pregnant women dosed with lopinavir and ritonavir compared to the safety described in non-pregnant adults, based on the review of these limited data.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of over 3,000 exposures to lopinavir containing regimens (including over 1,000 exposed in the first trimester), there was no difference between lopinavir and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolita Atlanta Congenital Defects Program. The prevalence of birth defects in live births was 2.1% (95% Cl: 1.4% to 3.0%) following first-trimester exposure to lopinavir-containing regimens and 3.0% (95% Cl: 2.4% to 3.8%) following second and third trimester exposure to lopinavir-containing regimens. Based on prospective reports from the APR of over 5,000 exposures to ritonavir containing regimens (including over 2,000 exposures in the first trimester) there was no difference between ritonavir and overall birth defects compared with the U.S. background rate (MACDP). The prevalence of birth defects in live births was 2.2% (95% CI: 1.7% to 2.8%) following firsttrimester exposure to ritonavir-containing regimens and 2.9% (95% Cl: 2.4% to 3.6%) following second and third trimester exposure to ritonavir- containing regimens. For both lopinavir and ritonavir, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5 fold increase in risk of overall birth defects and a 2 fold increase in risk of birth defects in the cardiovascular and Animal Data

Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence critically variations and skeletal ossification delays) occurred in rats administered lopinavir in combination with ritinavir (on gestation days 6 to 17) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7 times (for loninavir) and 1.8 times (for ritonavir) the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). In a pre-and post-natal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21)

No embryonic and fetal developmental toxicities were observed in rabbits administered lopinavir in combination with ritonavir (on gestation days 6 to 18) at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6 times (for lopinavir) and similar to (for ritonavir) the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily). 8.2 Lactation

Risk Summary 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. Because of the potential for: 1) HIV transmission (in HIV-negative infants), 2) developing viral resistance (in HIV- positive infants), and 3) adverse reactions in the breastfed infant, instruct mothers not to breastfed if they are receiving lopinavir

and ritonavir. 8.3 Females and Males of Reproductive Potential

Use of lopinavir and ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception [see Drug Interactions

Contraception

The safety, efficacy, and pharmacokinetic profiles of lopinavir and ritonavir in pediatric patients below the age of 14 days have not been established. Lopinavir and ritonavir should not be administered once daily in pediatric patients. An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/m² twice daily plus two NRTIs in HIV-infected infants ≥ 14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir AUC_{12} than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-1 RNA <400 copies/mL at Week 24 *[see* Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)].

Safety and efficacy in pediatric patients > 6 months of age was demonstrated in a clinical trial in 100 patients. The clinical trial was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve and experienced pediatric patients ages 6 months to 12 years. Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m² oral solution twice daily regimen without nevirapine and the 300/75 mg/m² oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine) [see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]. A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose lopinavir and ritonavir with or without concurrent NNRTI therapy (Group 1: $400/100 \text{ mg/m}^2$ twice daily $+ \ge 2 \text{ NRTIs}$; Group 2: $480/120 \text{ mg/m}^2$ twice

daily $+ \ge 1$ NRTI + 1 NNRTI) in 26 children and adolescents ≥ 2 years to < 18 years of age who had failed prior therapy. Patients also had saquinavir mesylate added to their regimen. This strategy was intended to assess whether higher than approved doses of lopinavir and ritonavir could overcome protease inhibitor cross-resistance. High doses of lopinavir and ritonavir exhibited a safety profile similar to those observed in previous trials; changes in HIV-1 RNA were less than anticipated; three patients had HIV-1 RNA <400 copies/mL at ses were noted in the eight patients who remained on treatment for 48 weeks [see Adverse Reactions (6.2), Clinical Pharmacology (12.3)]. A prospective multicenter, randomized, open-label study evaluated the efficacy and safety of twice-daily versus once-daily dosing of lopinavir and ritonavir tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, \geq 15 kg in weight, receiving cART that included lopinavir

and ritonavir. HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, efficacy (defined as the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL) was significantly higher in subjects receiving twice daily dosing compared to subjects receiving once daily dosing. The safety profile was similar between the two treatment arms although there was a greater incidence of diarrhea in the once daily treated subjects. 8.5 Geriatric Use

Clinical studies of lopinavir and ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they

respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and of lopinavir and ritonavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. 8.6 Hepatic Impairment

Lopinavir and ritonavir is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased [see Warnings and Precautions (5.4) and Clinical

Overdoses with lopinavir and ritonavir oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of lopinavir and ritonavir oral solution (520 mg lopinavir, approximately 10-fold above the recommended lopinavir dose) nine days prior. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure [see Warnings and Precautions (5.2)]. Healthcare professionals should be aware that lopinavir and ritonavir oral solution is highly concentrated and therefore, should pay special attention to accurate calculation of the dose of lopinavir and ritonavir, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young Lopinavir and ritonavir oral solution contains ethanol and propylene glycol. Ingestion of the product over the recommended dose by an infant or a young child could result in significant toxicity and could potentially be lethal.

Human experience of acute overdosage with lopinavir and ritonavir is limited. Treatment of overdose with lopinavir and ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with lopinavir and ritonavir. If indicated, elimination of unabsorbed drug should be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since lopinavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. However, dialysis can remove both ethanol and propylene alvool in the case of overdose with loninavir and ritonavir oral solution. 11 DESCRIPTION

Loninavir and ritonavir tablets, LISP are a co-formulation of Ioninavir and ritonavir Loninavir is an inhibitor of the HIV-1 protease. As ulated in lopinavir and ritonavir tablets USP, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir is chemically designated as $[1S-[1R^*,(R^*), 3R^*, 4R^*]]-N-[4-[[(2,6-dimethylphenoxy) acetyl]amino]-3-hydroxy-5-phenyl-1$ (phenylmethyl)pentyl]tetrahydro-alpha-(i-methylethyl)-2-oxo-((2H)-pyrimidineacetamide. Its molecular formula is C₃₇H₄₈N₄O₅, and its molecular weight is 628.80. Lopinavir is a white powder. It is very soluble to freely soluble in methanol, freely soluble in alcohol, soluble

Ritonavir is chemically designated as 10-hydroxy-2-methyl-5-(I-methylethyl)-I-[2-(I-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis (phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, $[5S\cdot(5R^*,8R^*,10R^*,11R^*)]$. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir is a white to light-tan, crystalline powder. It is freely soluble in methanol and in methy slightly soluble in acetonitrile, practically insoluble in water. Ritonavir has the following structural formula:

 Light yellow tablets containing 200 mg of lopinavir USP and 50 mg of ritonavir USP . Light yellow tablets containing 100 mg of lopinavir USP and 25 mg of ritonavir USP.

in isopropanol, practically insoluble in water. Lopinavir has the following structural formula:

The light yellow lopinavir and ritonavir tablets USP, 100 mg/25 mg and 200 mg/50 mg tablets contain the following inactive ingredients copovidone, sorbitan monolaurate, colloidal silicon dioxide, poloxamer 188, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, polyethylene glycol 400, polysorbate 80, titanium dioxide, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Lopinavir and ritonavir is a fixed-dose combination of HIV-1 antiviral druos lopinavir [see Microbiology (12.4)] and ritonavir. As co-

formulated in lopinavir and ritonavir, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

12.2 Pharmacodynamics Cardiac Electrophysiology

The effect of lopinavir and ritonavir on QTcF interval was evaluated in a placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 5.3 (8.1) and 15.2 (18.0) mseconds (msec) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily lopinavir and ritonavir, respectively. Lopinavir and ritonavir 800/200 mg twice daily resulted in a Day 3 mean C_{max} approximately 2-fold higher than the mean C_{max} observed with the approved once daily and twice daily lopinavir and ritonavir doses at steady state. The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 24.9 (21.5, 28.3) and 31.9 (28.5, 35.3) msec for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily lopinavir and ritonavir, respectively [see Warnings and Precautions (5.5, 5.6)].

12.3 Pharmacokinetics The pharmacokinetic properties of lopinavir are summarized in Table 13. The steady-state pharmacokinetic parameters of lopinavir are summarized in Table 14. Under fed conditions, lopinavir concentrations were similar following administration of lopinavir and ritonavir tablets to capsules with less pharmacokinetic variability. Under fed conditions (500 kcal, 25% from fat), lopinavir concentrations were

similar following administration of lopinavir and ritonavir capsules and oral solution Table 13. Pharmacokinetic Properties of Lopinavir

	1
Absorption	
T _{max} (hr) ^a	4.4 ± 0.8
Effect of meal (relative to fasting) Tablet Oral solution	↑19% ^b ↑130% ^b
Distribution	
% Bound to human plasma proteins	> 98
V _d /Fa (L)	16.9
Metabolism	
Metabolism	CYP3A
Elimination	
Major route of elimination	hepatic
t _{1/2} (h) ^a	6.9 ± 2.2
% of dose excreted in urine	10.4 ± 2.3
% of dose excreted in feces	82.6 ± 2.5
a. Lopinavir and ritonavir tablet b. Changes in AUC values	

Pharmacokinetic Parameter	Twice Daily ^a	Once Daily ^b
C _{max} (µg/mL)	9.8 ± 3.7	11.8 ± 3.7
C _{min} (µg/mL)	5.5 ± 2.7	1.7 ± 1.6
AUC _{tau} (μg•h/mL)	92.6 ± 36.7	154.1 ± 61.4

Specific Populations Gender, Race and Age

No gender or race related pharmacokinetic differences have been observed in adult patients. Lopinavir pharmacokinetics have not been studied in elderly patients Pediatric Patients

 $The \ 230/57.5 \ mg/m^2 \ twice \ daily \ regimen \ without \ nevirapine \ and \ the \ 300/75 \ mg/m^2 \ twice \ daily \ regimen \ with \ nevirapine \ provided$

Table 15. Lopinavir	Pharmacokinetic Data from Pediatric Clinic	cal Trials, Mean ± SD
C _{max} (µg/mL)	C _{min} (µg/mL)	AUC ₁₂ (μg•hr/m)
	Age ≥ 14 Days to < 6 Weeks Cohort (N = 9)	:
5.17 ± 1.84a	1.40 ± 0.48 ^a	43.39 ± 14.80a
ı	Age ≥ 6 Weeks to < 6 Months Cohort (N = 18	3):
9.39 ± 4.91a	1.95 ± 1.80a	74.50 ± 37.87a
	Age ≥ 6 Months to ≤ 12 years Cohort (N = 24	1):
8.2 ± 2.9b	3.4 ± 2.1 ^b	72.6 ± 31.1 ^b
10.0 ± 3.3c	3.6 ± 3.5°	85.8 ± 36.9°

The C_{12h} values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum in 12 HIV-infected pregnant women received lopinavir and ritonavir 400 mg/100 mg twice daily. Yet this decrease is not considered clinically relevant in patients with no documented lopinavir and ritonavir-associated resistance substitutions receiving 400 mg/100 mg twice daily [see Use in Specific Populations (8.1)]. Renal Impairment

b. Lopinavir and ritonavir oral solution 230/57.5 mg/m² twice daily without nevirapine (n=12)

c. Lopinavir and ritonavir oral solution 300/75 mg/m² twice daily with nevirapine (n=12)

Lopinavir pharmacokinetics have not been studied in patients with renal impairment; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal impairment. Hepatic Impairment

Multiple dosing of lopinavir and ritonavir 400/100 mg twice daily to HIV-1 and HCV co-infected patients with mild to moderate hepatic impairment (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-1 infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Lopinavir and ritonavir has not been studied in patients with severe hepatic impairment [see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)].

Lopinavir and ritonavir is an inhibitor of the P450 isoform CYP3A in vitro. Lopinavir and ritonavir does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations Lopinavir and ritonavir has been shown in vivo to induce its own metabolism and to increase the biotransformation of some drugs

metabolized by cytochrome P450 enzymes and by glucuronida The effects of co-administration of lopinavir and ritonavir on the AUC, C_{max} and C_{min} are summarized in Table 16 (effect of other drugs on lopinavir) and Table 17 (effect of lopinavir and ritonavir on other drugs). For information regarding clinical recommendations, see

Table 16. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for

	Re	commended Alterations in	Dose or Re	egimen		
Co-administered Drug	Dose of Co- administered Drug (mg)	Dose of Lopinavir and Ritonavir (mg)	n	Ratio (in combination with Co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Efavirenz ¹	600 at bedtime	400/100 capsule twice daily	11, 7 ³	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bedtime	500/125 tablet twice daily	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 at bedtime	600/150 tablet twice daily	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Etravirine	200 twice daily	400/100 mg twice day (tablets)	16	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)
Fosamprenavir ²	700 twice daily plus ritonavir 100 twice daily	400/100 capsule twice daily	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)

Co-administered Drug	Dose of Co- administered Drug (mg) Dose of Lopinavir and Ritonavir (mg)		n	Ratio (in combination with Co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00			
				C _{max}	AUC	C _{min}	
Ketoconazole	200 single dose	400/100 capsule twice daily	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)	
Nelfinavir	1000 twice daily	400/100 capsule twice daily	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)	
Nevirapine	200 twice daily steady-state	400/100 capsule twice daily	22, 19 ³	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)	
	7 mg/kg or 4 mg/kg once daily; twice daily 1 wk ⁵	(> 1 yr) 300/ 75 mg/m ² oral solution twice daily	12, 15 ³	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)	
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir ²	25/150/100 + dasabuvir 400	400/100 tablet twice daily	6	0.87 (0.76, 0.99)	0.94 (0.81, 1.10)	1.15 (0.93, 1.42)	
Omeprazole	40 once daily, 5 d	400/100 tablet twice daily, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)	
	40 once daily, 5 d	800/200 tablet once daily, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)	
Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)	
Ranitidine	150 single dose	400/100 tablet twice daily, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)	
	150 single dose	800/200 tablet once daily, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)	
Rifabutin	150 once daily	400/100 capsule twice daily	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)	
Rifampin	600 once daily	400/100 capsule twice daily	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)	
	600 once daily	800/200 capsule twice daily	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)	
	600 once daily	400/400 capsule twice daily	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)	
Rilpivirine	150 once daily	400/100 twice daily (capsules)	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)	
Ritonavir	100 twice daily	400/100 capsule twice daily	8, 21 ³	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)	
Tipranavir/ ritonavir	500/200 twice daily	400/100 capsule twice daily	21 69 ³	0.53 (0.40, 0.69)	0.45 (0.32, 0.63)	0.30 (0.17, 0.51)	
						0.48 ⁴ (0.40, 0.58)	

Reference for comparison is lopinavir/ritonavir 400/100 mg twice daily without efavirenz. 2 Data extracted from the U.S. prescribing information of co-administered drugs. Parallel group design

4 Drug levels obtained at 8 to 16 hours post dose

N/A = Not available.

Table 17. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Lopinavir and Ritonavir for nmended Alterations in Dose or Regimen

Ratio (in combination with Lopinavir and Ritonavir,

alone) of Co-administered Drug

Co-administered Drug	administered Drug (mg)	Lopinavir and n Ritonavir (mg)		alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00			
				C _{max}	AUC	C _{min}	
Bedaquiline ¹	400 single dose	400/100 twice daily	N/A	N/A	1.22 (1.11, 1.34)	N/A	
Efavirenz	600 at bedtime	400/100 capsule twice daily	11, 12 ³	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)	
Elbasvir/ grazoprevir ¹	50 once daily	400/100 twice	10	2.87 (2.29, 3.58)	3.71 (3.05, 4.53)	4.58 (3.72, 5.64)	
	200 once daily	daily	13	7.31 (5.65, 9.45)	12.86 (10.25, 16.13)	21.70 (12.99, 36.25)	
Ethinyl Estradiol	35 µg once daily (Ortho Novum®)	400/100 capsule twice daily	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)	
Etravirine	200 twice daily	400/100 tablet twice day	16	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)	
Fosamprenavir ¹	700 twice daily plus ritonavir 100 twice daily	400/100 capsule twice daily	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)	
Indinavir	600 twice daily combo nonfasting vs. 800 three times daily alone fasting	400/100 capsule twice daily	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)	
Ketoconazole	200 single dose	400/100 capsule twice daily	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A	
Maraviroc ¹	300 twice daily	400/100 twice daily	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)	
Methadone	5 single dose	400/100 capsule twice daily	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A	
Nelfinavir	1000 twice daily combo vs. 1250 twice daily alone	400/100 capsule twice daily	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)	
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)	
Nevirapine	200 once daily twice daily	400/100 capsule twice daily	5, 6 ³	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)	
Norethindrone	1 once daily (Ortho Novum®)	400/100 capsule twice daily	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)	
Ombitasvir/ paritaprevir/ ritonavir+ dasabuvir ¹	25/150/100 + dasabuvir 400	400/100 tablet twice daily	6	1.14 (1.01, 1.28) 2.04 (1.30, 3.20) 1.55 (1.16, 2.09) 0.99 (0.75, 1.31)	1.17 (1.07, 1.28) 2.17 (1.63, 2.89) 2.05 (1.49, 2.81) 0.93 (0.75, 1.15)	1.24 (1.14, 1.34) 2.36 (1.00, 5.55) 5.25 (3.33, 8.28) 0.68 (0.57, 0.80)	
Pitavastatin ¹	4 once daily	400/100 tablet twice daily	23	0.96 (0.84-1.10)	0.80 (0.73-0.87)	N/A	
Pravastatin	20 once daily	400/100 capsule twice daily	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A	
Rifabutin	150 once daily combo vs. 300 once daily alone	400/100 capsule twice daily	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)	
25- <i>O</i> -desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)	
Rifabutin + 25- <i>O</i> -desacetyl rifabutin				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)	
Rilpivirine	150 once daily	400/100 capsules twice daily	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)	
Rosuvastatin ²	20 once daily	400/100 tablet twice daily	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)	
Tenofovir alafenamide ¹	10 once daily	800/200 tablet once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	N/A	
Tenofovir disoproxil fumarate ¹	300 once daily	400/100 capsule twice daily	24	No Change	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)	

3 Parallel group design

N/A = Not available. 12.4 Microbiology

Mechanism of Action Lopinavir, an inhibitor of the HIV-1 protease, prevents cleavage of the viral Gag-Pol polyprotein, resulting in the production of immature,

non-infectious viral particles.

In the absence of human serum, the mean 50% effective concentration (EC_{50}) values of lopinavir against five different HIV-1 subtype B laboratory strains in lymphoblastic cell lines ranged from 10 to 27 nM (0.006 to 0.017 μ g/mL, 1 μ g/mL = 1.6 μ M), and ranged from 4 to 11 nM (0.003 to 0.007 μ g/mL) against several HIV-1 subtype B clinical isolates in peripheral blood lymphocytes (n = 6). In the presence of 50% human serum, the mean EC₅₀ values of lopinavir against these five HIV-1 laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 μ g/mL), representing a 7 to 11-fold attenuation. The EC₅₀ values of lopinavir against three different HIV-2 strains ranged from 12 to 180 nM (0.008 to 113 μg/mL).

HIV-1 isolates with reduced susceptibility to lopinavir have been selected in cell culture. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in cell culture. In a study of 653 antiretroviral treatment-naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV-1 RNA >400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No specific amino acid substitutions could be associated with resistance to lopinavir and ritonavir in the virus from 37 evaluable lopinavir and ritonavir-treated patients. The selection of resistance to lopinavir and ritonavir in antiretroviral treatment-naïve pediatric patients (Study 940) appears to be consistent with that seen in adult

patients (Study 863). Resistance to lopinavir and ritonavir has been noted to emerge in patients treated with other protease inhibitors prior to lopinavir and ritonavir therapy. In studies of 227 antiretroviral treatment-naïve and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with lopinavir and ritonavir for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. All four of these patients had previously received treatment with at least one protease inhibitor and had at least 4 substitutions associated with protease inhibitor resistance immediately prior to lopinavir and ritonavir therapy. Following viral rebound, isolates from these patients all contained additional substitutions, some of which are recognized to be associated with protease inhibitor resistance. Cross-resistance - Nonclinical Studies

Varying degrees of cross-resistance have been observed among HIV-1 protease inhibitors. The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined (Table 18).

ble 18. Susceptibility Reduction to Lopinavir Against Isolates from Patients Previously Treated With a Single Protease Inhibitor					
Susceptibility reduced by >4 fold Susceptibility reduced to LPV					
Indinavir (n=16)	5.7 fold				
Nelfinavir (n=13)	<4 fold				
Ritonavir (n=3)	8.32 fold				
Saquinavir (n=4)	<4 fold				

Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following section

<u>Clinical Studies - Antiviral Activity of Lopinavir and Ritonavir in Patients with Previous Protease Inhibitor Therapies</u> The clinical relevance of reduced susceptibility in cell culture to lopinavir has been examined by assessing the virologic response to lopinavir and ritonavir therapy in treatment-experienced patients, with respect to baseline viral genotype in three studies and baseline viral phenotype in one study. Virologic response to lopinavir and ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F//R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Table 19 shows the 48-week virologic response (HIV-1 RNA <400 copies/mL) according to the number of the above protease inhibitor resistance-

associated substitutions at baseline in studies 888 and 765 [see Clinical Studies (14.2) and (14.3)] and study 957 (see below). Once daily administration of lopinavir and ritonavir for adult patients with three or more of the above substitutions is not recommended

Number of protease inhibitor substitutions at baseline ¹	Study 888 (Single protease inhibitor-experienced ² , NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced ³ , NNRTI-naïve) n=56	Study 957 (Multiple protease inhibitor-experienced ⁴ , NNRTI-naïve) n=50
0 to 2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3 to 5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	N/A	1/4 (25%)
2 43% indinavir, 42% nelfi 3 41% indinavir, 38% nelfi	in the analysis included L10F/I/R/V, K: navir, 10% ritonavir, 15% saquinavir navir, 4% ritonavir, 16% saquinavir. navir, 80% ritonavir, 70% saquinavir		3V, 154L/T/V, V82A/C/F/S/T, and 184V

Virologic response to loninavir and ritonavir therapy with respect to phenotypic susceptibility to loninavir at baseline was examined in Study 957. In this study 56 NNRTI-naïve patients with HIV-1 RNA >1,000 copies/mL despite previous therapy with at least two protease inhibitors selected from indinavir, nelfinavir, ritonavir, and saquinavir were randomized to receive one of two doses of lopinavir and ritonavir in combination with efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs). The EC₅₀ values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type EC₅₀ value. Fifty-five percent (31/56) of these baseline isolates displayed >4-fold reduced susceptibility to lopinavir. These 31 isolates had a median reduction in lopinavir susceptibility of 18-fold. Response to therapy by baseline lopinavir susceptibility is shown in Table 20.

Lopinavir susceptibility ² at baseline	HIV-1 RNA <400 copies/mL (%)	HIV-1 RNA <50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
> 10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure (based on AUC_{0-24hr} measurement) at the recommended dose of 400/100 mg lopinavir and ritonavir twice daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg lopinavi and ritonavir twice daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg lopinavir and ritonavir twice daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes. Impairment of Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

14 CLINICAL STUDIES 14.1 Adult Patients without Prior Antiretroviral Therapy

2.6 to 6.8 log₁₀ copies/mL)

Study 863: Lopinavir and Ritonavir Capsules twice daily + stavudine + lamivudine compared to nelfinavir three times daily + stavudine + Study 863 was a randomized, double-blind, multicenter trial comparing treatment with lopinavir and ritonavir capsules (400/100 mg twice daily) plus stavudine and lamivudine versus nelfinavir (750 mg three times daily) plus stavudine and lamivudine in 653 antiretroviral treatment naïve patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4+ cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range:

Treatment response and outcomes of randomized treatment are presented in Table 21

Outcome	Lopinavir and Ritonavir+d4T+3TC (N = 326)	Nelfinavir+d4T+3TC (N = 327)	
Responder ¹	75%	62%	
Virologic failure ² Rebound Never suppressed through Week 48	9% 7% 2%	25% 15% 9%	
Death	2%	1%	
Discontinued due to adverse events	4%	4%	
Discontinued for other reasons ³	10%	8%	

2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48. 3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through Week 48, including patients who discontinued subsequent to virologic failure, was 17% in the lopinavir and ritonavir arm and 24% in the nelfinavir arm Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir and ritonavir arm compared to the nelfinavir arm with HIV-1 RNA < 400 copies/mL (75% vs. 62%, respectively) and HIV-1 RNA < 50 copies/mL (67% vs.

52%, respectively). Treatmen	t response by bas	seline HIV-1 RNA I	evel subgroups is	presented in Tabl	e 22.	
Table 2	22. Proportion of	Responders Thro	ugh Week 48 by I	Baseline Viral Loa	ıd (Study 863)	
Baseline Viral Load (HIV- 1 RNA copies/mL)	Lopinav	Lopinavir and Ritonavir +d4T+3TC		C Nelfinavir +d4T+3TC		
	<400 copies/mL ¹	<50 copies/mL ²	n	<400 copies/mL ¹	<50 copies/mL ²	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	81%	73%	79	67%	54%	79
> 100 000 to < 250 000	750/	6.40/	02	600/	470/	70

44%

2 Patients achieved HIV-1 RNA < 50 copies/mL at Week 48. ough 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 207 cells/mm³ for the lopinavir and ritonavir arm

72% 60% 82

Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

≥ 250.000

Study 730: Lopinavir and Ritonavir Tablets once daily + tenofovir DF + emtricitabine compared to Lopinavir and Ritonavir Tablets twice daily + tenofovir DF + emtricitabine Study 730 was a randomized, open-label, multicenter trial comparing treatment with lopinavir and ritonavir 800/200 mg once daily plus tenofovir DF and emtricitabine versus lopinavir and ritonavir 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Patients were randomized in a 1:1 ratio to receive either lopinavir and ritonavir 800/200 mg once daily (n = 333) or lopinavir and ritonavir 400/100 mg twice daily (n = 331). Further stratification within each group was 1:1 (tablet vs. capsule). Patients administered the capsule were switched to the tablet formulation at Week 8 and maintained on their randomized dosing schedule. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled solicular. Lateria were daministered entiritationite zoot in yorke daniy and tendorum 1 500 mg office and parties was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ cell count was 216 cells/mm³ (range: 20 to 775 cells/mm³) and mean baseline plasma HIV-1 RNA was 5.0 log₁₀ copies/mL (range: 1.7 to 7.0 log₁₀ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 23.

Table 23. Outcomes of Randomized Treatment Through Week 48 (Study 730)			
Outcome	Lopinavir and Ritonavir Once Daily + TDF + FTC (n = 333)	Lopinavir and Ritonavir Twice Daily + TDF + FTC (n = 331)	
Responder ¹	78%	77%	
Virologic failure ² Rebound Never suppressed through Week 48	10% 5% 5%	8% 5% 3%	
Death	1%	<1%	
Discontinued due to adverse events	4%	3%	
Discontinued for other second	00/	440/	

1 Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.
2 Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48. 3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons

Through 48 weeks of therapy, 78% in the lopinavir and ritonavir once daily arm and 77% in the lopinavir and ritonavir twice daily arm achieved and maintained HIV-1 RNA 50 copies/mL (95% confidence interval for the difference, -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells/mm³ for the lopinavir and ritonavir once daily arm and 198 cells/mm³ for the lopinavir and ritonavir

twice daily arm. 14.2 Adult Patients with Prior Antiretroviral Therapy Study 888: Lopinavir and Ritonavir Capsules twice daily + nevirapine + NRTIs compared to investigator- selected protease inhibitor(s) +

Study 888 was a randomized, open-label, multicenter trial comparing treatment with lopinavir and ritonavir capsules (400/100 mg twice daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitor in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4+ cell count was 322 cells/mm³ (range: 10 to 1059 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.1 log₁₀ copies/mL (range: 2.6 to 6.0 log₁₀ copies/mL).

eatment response and outcomes of randomized treatment through Week 48 are presented in Table 24

Outcome	Lopinavir and Ritonavir + nevirapine + NRTIs (n = 148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n = 140)
Responder ¹	57%	33%
Virologic failure ² Rebound Never suppressed through Week 48	24% 11% 13%	41% 19% 23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons ³	14%	13%

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48. ound and failure to a 3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reason: Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the lopinavir and ritonavir arm

compared to the investigator-selected protease inhibitor(s) arm with HIV- 1 RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 111 cells/mm3 for the lopinavir and ritonavir arm and 112 cells/mm3 for the investigator-selected protease inhibitor(s) arm Study 802: Lopinavir and Ritonavir Tablets 800/200 mg Once Daily Versus 400/100 mg Twice Daily when Co-administered with Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors in Antiretroviral- Experienced, HIV-1 Infected Subjects M06-802 was a randomized open-label study comparing the safety, tolerability, and antiviral activity of once daily and twice daily dosing of lopinavir and ritonavir tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Of the enrolled subjects, 55% on both treatment arms had not been previously treated with a protease inhibitor and 81 to 88% had received prior NNRTIs as part of their anti-HIV treatment regimen. Patients were randomized in a 1:1 ratio to receive either lopinavir and ritonavir 800/200 mg once daily (n = 300) or lopinavir and ritonavir 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside nucleotide reverse transcriptase inhibitors selected by the investigator. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian, and 66% were male. Mean baseline CD4+ cell count was 254 cells/mm³ (range: 4 to 952 cells/mm³) and mean baseline

plasma HIV-1 RNA was 4.3 log₁₀ copies/mL (range: 1.7 to 6.6 log₁₀ copies/mL).

Treatment response and outcomes of randomized trea	atment through Week 48 are presented in	Table 25.		
Table 25. Outcomes of Randomized Treatment Through Week 48 (Study 802)				
Outcome	Lopinavir and Ritonavir Once Daily + NRTIs (n = 300)	Lopinavir and Ritonavir Twice Daily + NRTIs (n = 299)		
Virologic Success (HIV-1 RNA <50 copies/mL)	57%	54%		
Virologic failure ¹	22%	24%		
No virologic data in Week 48 window				
Discontinued study due to adverse event or death ²	5%	7%		
Discontinued study for other reasons ³	13%	12%		
Missing data during window but on study	3%	3%		

1 Includes patients who discontinued prior to Week 48 for lack or loss of efficacy and patients with HIV-1 RNA \geq 50 copies/mL at 2 Includes patients who discontinued due to adverse events or death at any time from Day 1 through Week 48 if this resulted in no ologic data on treatment at Week 48. 3 Includes withdrawal of consent, loss to follow-up, non-compliance, protocol violation and other reasons.

Through 48 weeks of treatment, the mean change from baseline for CD4 + cell count was 135 cells/mm3 for the once daily group and 122

cells/mm3 for the twice daily group. 14.3 Other Studies Supporting Approval in Adult Patients Study 720: Lopinavir and ritonavir twice daily + stavudine + lamivudine

Study 765: Lopinavir and ritonavir twice daily + nevirapine + NRTIs Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) were randomized, blinded, multi-center trials evaluating treatment with lopinavir and ritonavir at up to three dose levels (200/100 mg twice daily [720 only], 400/100 mg twice daily, and 400/200 mg twice daily). In Study 720, all patients switched to 400/100 mg twice daily between Weeks 48 to 72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD4+ cell counts for patients in study 720 and study 765 were 338 (3 to 918) and 372 (72 to 807) cells/mm³, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) log₁₀ copies/mL, respectively. Through 360 weeks of treatment in study 720, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 61% (59%) [n =

100]. Among patients completing 360 weeks of treatment with CD4+ cell count measurements [n=60], the mean (median) increase in CD4+ cell count was 501 (457) cells/mm³. Thirty-nine patients (39%) discontinued the study, including 13 (13%) discontinuations due to adverse reactions and 1 (1%) death. Through 144 weeks of treatment in study 765, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD4+ cell count was 212 cells/mm³. Twenty-seven patients (39%) discontinued the study,

including 5 (7%) discontinuations secondary to adverse reactions and 2 (3%) deaths. 14.4 Pediatric Studies

Study 1030 was an open-label, multicenter, dose-finding trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/m² twice daily plus 2 NRTIs in HIV-1 infected infants ≥14 days and <6 months of age. Ten infants, ≥14 days and <6 wks of age, were enrolled at a median (range) age of 5.7 (3.6 to 6.0) weeks and all completed 24 weeks. At

entry, median (range) HIV-1 RNA was 6.0 (4.7 to 7.2) log₁₀ copies/mL. Seven of 10 infants had HIV-1 RNA <400 copies/mL at Week 24. At entry, median (range) CD4+ percentage was 41 (16-59) with a median decrease of 1% (95% CI: -10, 18) from baseline to week 24 in 6 infants with available data. Twenty-one infants, between 6 weeks and 6 months of age, were enrolled at a median (range) age of 14.7 (6.9 to 25.7) weeks and 19 of 21 infants completed 24 weeks. At entry, median (range) HIV RNA level was 5.8 (3.7 to 6.9) \log_{10} copies/mL. Ten of 21 infants had HIV RNA <400 copies/mL at Week 24. At entry, the median (range) CD4+ percentage was 32 (11 to 54) with a median increase of 4% (95% CI: -1, 9) from baseline to week 24 in 19 infants with available data [see Clinical Pharmacology (12.3) for pharmacokinetic results].

Study 940 was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of lopinavir and ritonavir oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naïve patients also received lamivudine and stavudine. erienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After

analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m² dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4+ cell count was 838 cells/mm³ and mean baseline mà HIV-1 RNA was 4.7 log₁₀ cópies/mL. ough 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV-1 RNA < 400 copies/mL was 80% for

antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD4+ cell count was 404 cells/mm³ for antiretroviral naïve and 284 cells/mm³ for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse reaction, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-1 related event. Dose selection in pediatric patients was based on the following:

 Among patients 14 days to 6 months of age receiving 300/75 mg/m² twice daily without nevirapine, plasma concentrations were lower than those observed in adults or in older children. This dose resulted in HIV-1 RNA < 400 copies/mL in 55% of patients (70% in those initiating treatment at <6 weeks of age).

Among patients 6 months to 12 years of age, the 230/57.5 mg/m² oral solution twice daily regimen without nevirapine and the 300/75 mg/m² oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine). These doses resulted in treatment benefit (proportion of patients with HIV-1 RNA < 400 copies/mL) similar to that seen in the adult clinical trials. Among patients 12 to 18 years of age receiving 400/100 mg/m² or 480/120 mg/m² (with efavirenz) twice daily, plasma
concentrations were 60 to 100% higher than among 6 to 12 year old patients receiving 230/57.5 mg/m². Mean apparent
clearance was similar to that observed in adult patients receiving standard dose and in patients 6 to 12 years of age. Although changes in HIV-1 RNA in patients with prior treatment failure were less than anticipated, the pharmacokinetic data supports use of similar dosing as in patients 6 to 12 years of age, not to exceed the recommended adult dose.

 For all age groups, the body surface area dosing was converted to body weight dosing using the patient's prescribed lopinavir 16 HOW SUPPLIED/STORAGE AND HANDLING

Lopinavir and ritonavir tablets, USP are available in the following strengths and package sizes: Lopinavir and Ritonavir Tablets, USP containing 100 mg Iopinavir and 25 mg ritonavir are light yellow film-coated capsule shaped tablets debossed with 'D91' on one side and plain on other side.

Lopinavir and Ritonavir Tablets, USP containing 200 mg lopinavir and 50 mg ritonavir are light yellow film-coated ovaloid tablets ossed with 'X' on one side and '28' on other side. Bottles of 120 NDC 65862-333-08 Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in original container or USP equivalent tight container (250 mL or less). For patient use: exposure of this product to high humidity outside the original container or USP equivalent tight container (250 mL or less) for longer than 2 weeks is not recommended

17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide)

General Administration Information [see Dosage and Administration (2)]: · Advise patients to pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or

Advise patients and caregivers that the oral solution should be administered using the calibrated dosing cup (supplied) or oral Advise caregivers to inform their healthcare provider if the child's weight changes in order to make sure that the child's lopinavir and

ritonavir dose is adjusted as needed. Inform patients and caregivers that lopinavir and ritonavir tablets may be taken with or without food but lopinavir and ritonavir oral solution should be taken with food to enhance absorption.

Advise patients to remain under the care of a healthcare provider while using lopinavir and ritonavir and to take lopinavir and

ritonavir in combination with other antiretroviral drugs as prescribed.

Advise patients not to alter the dose or discontinue therapy without consulting with their healthcare provider. If a dose of lopinavir and ritonavir is missed patients 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. nform patients that it is important to take lopinavir and ritonavir on a regular dosing schedule as directed and to avoid missing

doses as that can result in development of resistance. Inform patients that there may be a greater chance of developing diarrhea with the once daily regimen as compared with the twice Inform patients that lopinavir and ritonavir is not a cure for HIV-1 infection and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections **Drug Interactions**

Inform patients that lopinavir and ritonavir may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products such as St. John's Wort [see Contraindications (4), Warnings and Precautions (5.1) and Drug Interactions (7)]. <u>Pancreatitis</u> Advise patients that pancreatitis has been observed in patients receiving lopinavir and ritonavir and to alert their healthcare provider if they experience symptoms such as nausea, vomiting or abdominal pain [see Warnings and Precautions (5.3)]. Skin Rash Inform nations that skin rash ranging in severity from mild to toxic epidermal necrolysis (TEN). Stevens-Johnson syndrome, erythema

multiforme, urticaria, and angioedema have been reported in patients receiving lopinavir and ritonavir or its components lopinavir and/ or ritonavir. Advise patients to contact their healthcare provider if they develop a rash while taking lopinavir and ritonavir [see Adverse] Reactions (6.1)]. Pre-existing liver disease including Hepatitis B or C can worsen with use of lopinavir and ritonavir. This can be seen as worsening of transaminase elevations or hepatic decompensation. Advise patients that their liver function tests will need to be monitored closely

especially during the first several months of lopinavir and ritonavir treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin [see Warnings and Precautions (5.4)1. QT and PR Interval Prolongation Advise patients that lopinavir and ritonavir may produce changes in the electrocardiogram (e.g., PR and/or QT prolongation) and to consult their healthcare provider if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness [see Warnings and Precautions (5.5, 5.6)].

Diabetes Mellitus/Hyperglycemia Advise patients that new onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during lopinavir and ritonavir use. Advise patients to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on lopinavir

and ritonavir as they may require a change in their diabetes treatment or new treatment [see Warnings and Precautions (5.7)]. Immune Reconstitution Syndrome Advise patients that immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including lopinavir and ritonavir [see Warnings and Precautions (5.8)].

Advise patients that treatment with lopinavir and ritonavir therapy can result in substantial increases in the concentration of total cholesterol and triglycerides [see Warnings and Precautions (5.9)]. Fat Redistribution Advise patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time [see Warnings and Precautions (5.10)]. Patients with Hemophilia

Advise patients with hemophilia that they may experience increased bleeding when treated with protease inhibitors such as lopinavir and ritonavir [see Warnings and Precautions (5.11)]. Pregnancy Exposure Registry Inform patients that there is an antiretroviral pregnancy registry that monitors fetal outcomes of pregnant women exposed to lopinavir and ritonavir [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 breast milk [see Use in Specific

Populations (8.2)1. The brands listed are trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited. The makers of these brands are not affiliated with and do not endorse Aurobindo Pharma Limited or its products. $\textbf{Dispense with Medication Guide available at:} \underline{\textbf{www.aurobindousa.com/product-medication-guides}}.$

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Issued: February 2020

MEDICATION GUIDE Lopinavir and Ritonavir Tablets USP (loe PIN a vir and ri toe' na veer)

What is the most important information I should know about lopinavir and ritonavir tablets?

Lopinavir and ritonavir tablets may cause serious side effects, including Interactions with other medicines. It is important to know the medicines that should not be taken with lopinavir and ritona tablets. For more information, see "Who should not take lopinavir and ritonavir tablets Side Effects in babies taking lopinavir and ritonavir oral solution. Lopinavir and ritonavir oral solution contains alcohol (ethano

and propylene glycol. Call your healthcare provider right away if your baby appears too sleepy or their breathing changes Inflammation of your pancreas (pancreatitis). Lopinavir and ritonavir tablets can cause pancreatitis which may be serious and may lead to death. People who have high levels of a certain fat (triglycerides) have a risk for developing pancreatitis. If you have advanced HIV-1 disease, you may have an increased risk of high triglyceride levels in your blood, and pancreatitis. If you have a history of pancreatitis, you may have an increased risk of it coming back again during treatment with lopinavir and ritonavir tablets. Tell your healthcare provider if you have any signs or symptoms of pancreatitis including:

o stomach-area (abdominal) pain

Liver problems. Liver problems, including death, can happen in people who take lopinavir and ritonavir tablets. Your healthcare provider should do blood tests before and during your treatment with lopinavir and ritonavir tablets to check your liver function. If you have Hepatitis B or Hepatitis C, or other liver problems, you may have an increased risk for developing new or worsening of er problems during treatment with lopinavir and ritonavir tablets. Tell your healthcare provider right away if you have any signs

o loss of appetite o pale colored stools yellow skin and whites of eyes (jaundice) itchv skin o stomach area (abdominal) pain

Changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an EKG (electrocardiogram and can lead to serious heart problems. Your risk for these problems may be higher if you:

o have a history of abnormal heart rhythm or certain types of heart problem o take other medicines that can affect your heart rhythm during treatment with lopinavir and ritonavir tablets.

Tell your healthcare provider right away if you have any of these symptoms:

 lightheadedness sensation of abnormal heartbeats See "What are the possible side effects of lopinavir and ritonavir tablets?" for more information about serious side effects.

deficiency Virus-1 (HIV-1) infection in adults and children 14 days of age and older. HIV is the virus that causes AIDS (Acquired

It is not known if lopinavir and ritonavir is safe and effective in children under 14 days old. Who should not take lopinavir and ritonavir tablets? Do not take lopinavir and ritonavir tablets if you:

are allergic to lopinavir, ritonavir, or any of the ingredients in lopinavir and ritonavir tablets. See the end of this Medication Guide for a complete list of ingredients in lopinavir and ritonavir tablets. if you take any of the following medicines: apalutamide

have high cholesterol in your blood.

ranolazine colchicine, if you have kidney or liver problems.

pimozide ergot containing medicines including: ergotamine tartrate methylergonovine

elbasvir/grazoprevir Iovastatin sildenafil (Revatio®), when used for the treatment of pulmonary arterial hypertension

 St. John's Wort (Hypericum perforatum[®]) rious problems can happen if you or your child takes any of the medicines listed above with lopinavir and ritonavir tablets Before taking lopinavir and ritonavir tablets, tell your healthcare provider about all of your medical conditions, including if you: have ever had a serious skin rash or an allergic reaction to medicines that contain lopinavir or ritonavir.

have or had pancreas problems.
have liver problems, including Hepatitis B or Hepatitis C. have any heart problems, including if you have a condition called Congenital Long QT Syndrome. have low potassium in your blood.

have hemophilia. Lopinavir and ritonavir tablets may cause increased bleeding, are pregnant or plan to become pregnant. It is not known if lopinavir and ritonavir tablets will harm your unborn baby. Lopinavir and ritonavir oral solution contains alcohol (ethanol) and propylene glycol. You should not take lopinavir and ritonavir oral solution during pregnancy because there is no safe level of alcohol exposure during pregnancy. Tell your healthcare provider if you become pregnant during treatment with lopinavir and ritonavir.

Lopinavir and ritonavir tablets may reduce how well hormonal birth control works. Females who may become pregnant

should use another effective form of birth control or an additional barrier method of birth control during treatment with Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of the pregnancy 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.

are breastfeeding or plan to breastfeed. Do not breastfeed if you take lopinavir and ritonavir tablets.

You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk to your healthcare provider about the best way to feed your baby. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Many medicines interact with lopinavir and ritonavir tablets. 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 lopinavir and ritonavir tablets

Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take lopinavir and ritonavir tablets with other medicines. Your healthcare provider may need to change the dose of other medicines during treatment with lopinavir and ritonavir tablets. How should I take lopinavir and ritonavir tablets?

If you are taking both didanosine and lopinavir and ritonavir tablets:

Take lopinavir and ritonavir tablets every day exactly as prescribed by your healthcare provide Stay under the care of your healthcare provider during treatment with lopinavir and ritonavir tablets. Do not change your treatment or stop treatment without first talking with your healthcare provider.

Swallow lopinavir and ritonavir tablets whole. Do not chew, break, or crush lopinavir and ritonavir tablets. Lopinavir and ritonavir tablets can be taken with or without food.

o You should not take lopinavir and ritonavir tablets on a 1 time each day dose schedule. o Avoid use of lopinavir and ritonavir oral solution. If your child is prescribed lopinavir and ritonavir tablets:

Take didanosine either 1 hour before or 2 hours after taking lopinavir and ritonavir oral solution.

Didanosine can be taken at the same time as lopinavir and ritonavir tablets, without food.

o Tell your healthcare provider if your child's weight changes. Lopinavir and ritonavir tablets should not be given to children on a 1 time each day dose schedule. When giving lopinavir and o Use the dosing cup (supplied) or an oral syringe with mL (millitler) markings to give the prescribed dose of lopinavir and ritonavir tablets to your child, give lopinavir and ritonavir and extensive propriets of the prescribed dose of lopinavir and ritonavir oral solution to your child. Your pharmacist should provide an oral syringe to you.

Lopinavir and ritonavir oral solution school provide glycol and a large amount of alcohol (ethanol). Lopinavir and ritonavir oral solution should not be given to babies younger than 14 days of age unless your healthcare provider thinks it is given to be the control or the provider thinks it is given to be the control or the provider thinks it is given to be the control or the provider thinks it is given to be the control or the provider thinks it is given to be the control or the provider thinks it is given to be the control or the provider thinks it is given to be the provider thinks it is given to be the provider thinks it is given to be the provider thinks in the provider thinks it is given to be the

is right for your baby. You may have a greater chance of getting diarrhea if you take lopinavir and ritonavir tablets 1 time each day than if you take it 2 Do not miss a dose of lopinavir and ritonavir tablets. This could make the virus harder to treat. If you forget to take lopinavir and ritonavir tablets, take the missed dose right away. If it is almost time for your next dose, do not take the missed dose, Instead, $follow\ your\ regular\ dosing\ schedule\ by\ taking\ your\ next\ dose\ at\ its\ regular\ time.\ \textbf{\textbf{Do}\ not}\ take\ more\ than\ one\ dose\ of\ lopinavir\ and$

If you or your child take more than the prescribed dose of lopinavir and ritonavir tablets, call your healthcare provider or go to the nearest emergency room right away. What are the possible side effects of lopinavir and ritonavir tablets? opinavir and ritonavir tablets can cause serious side effects, including:

See "What is the most important information I should know about lopinavir and ritonavir tablets?" Diabetes and high blood sugar (hyperglycemia). You may develop new or worsening diabetes or high blood sugar during treatment with lopinavir and ritonavir tablets. Tell your healthcare provider if you get any of the following signs or symptoms urinate more often than usual unusual weight loss increase in your blood sugar levels Your healthcare provider may need to start you on medicine to treat high blood sugar or change your diabetes medicines.

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. Call your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

Increases in certain fat (triglycerides and cholesterol) levels in your blood. Large increases of triglycerides and cholesterol can be seen in blood test results of some people who take lopinavir and ritonavir tablets. Your healthcare provider should do blood tests to check your cholesterol and triglyceride levels before you start taking lopinavir and ritonavir tablets and during your

Changes in body fat can happen in some people who take antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle 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 at this time. Increased bleeding in people with hemophilia. Some people with hemophilia have increased bleeding with lopinavir and

Skin rash, which can be severe, can happen in people who take lopinavir and ritonavir tablets. Tell your healthcare provider if you have a history of skin rash with other medicine used to treat your HIV-1 infection or if you get any skin rash during treatment with lopinavir and ritonavir tablets.

nmon side effects of lopinavir and ritonavir tablets include increased fats in blood (triglycerides or cholesterol)

 nausea These are not all of the possible side effects of lopinavir and ritonavir tablets. For more information, ask your healthcare provider o

Lopinavir and ritonavir tablets: Store lopinavir and ritonavir tablets at room temperature, between 68° to 77°F (20° to 25°C). Store lopinavir and ritonavir tablets in the original containe

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Do not keep lopinavir and ritonavir tablets out of the container it comes in for longer than 2 weeks, especially in areas where there Keep the container closed tightly.

How should I store loninavir and ritonavir tablets?

What are the ingredients in lopinavir and ritonavir tablets?

Active ingredients: lopinavir and ritonavir

Keep lopinavir and ritonavir tablets and all medicines out of the reach of children General information about the safe and effective use of lopinavir and ritonavir tablets. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lopinavir and ritonavi tablets for a condition for which it was not prescribed. Do not give lopinavir and ritonavir tablets to other people, even if they have the same condition you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about lopinavir and ritonavir tablets that is written for health

Inactive ingredients: ovidone, sorbitan monolaurate, colloidal silicon dioxide, poloxamer 188, and sodium stearyl fumarate. The following are the ngredients in the film coating: hypromellose, polyethylene glycol 400, polysorbate 80, titanium dioxide, and ferric oxide yellov

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