HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KALETRA safely and effectively. See full prescribing information for KALETRA.

KALETRA (lopinavir and ritonavir) tablet, for oral use
KALETRA (lopinavir and ritonavir) oral solution
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Contraindications (4)	11/2016
Warnings and Precautions	11/2016
Diabetes Mellitus/Hyperglycemia (5.7)	

INDICATIONS AND USAGE

KALETRA is an 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)
Adults (2.2):
- Total recommended daily dosage is 800/200 mg given once or twice daily.
- KALETRA can be given as once daily or twice daily regimen. See Full Prescribing Information for details.
- KALETRA 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, 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. (2.4, 8.1, 12.3)

Pediatric Patients (14 days and older) (2.3):
- KALETRA 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 KALETRA may be needed when co-administering with efavirenz, nevirapine, or nelfinavir. (2.2, 2.3, 7.3)
- KALETRA 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 (2.3, 5.2)

Pregnancy (2.4):
- 400/100 mg twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions.
- There are insufficient data to recommend a KALETRA dose for pregnant patients with any documented KALETRA-associated resistance substitutions.
- No dose adjustment of KALETRA is 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)
- Oral solution: 80 mg lopinavir and 20 mg ritonavir per milliliter (3)

CONTRAINDICATIONS

- Hypersensitivity to KALETRA (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urticaria, angioedema) or any of its ingredients, including ritonavir. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- Co-administration with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross resistance. (4)

WARNINGS AND PRECAUTIONS

The following have been observed in patients receiving KALETRA:
- The concomitant use of KALETRA and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)
- Toxicity in preterm neonates: KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established. (2.3, 5.2).
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.3)
- 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. (5.1, 5.5, 12.3)
- 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), redistribution/accumulation of body fat. (5.10)
- 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)

ADVERSE REACTIONS

Commonly reported adverse reactions to KALETRA included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Co-administration of KALETRA 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)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).

The following points should be considered when initiating therapy with KALETRA:

- The use of other active agents with KALETRA is associated with a greater likelihood of treatment response *[see Microbiology (12.4)* and *Clinical Studies (14)]*.
- Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA *[see Microbiology (12.4)]*. The number of baseline lopinavir resistance-associated substitutions affects the virologic response to KALETRA *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Recommendations

KALETRA tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed. KALETRA oral solution must be taken with food.

2.2 Dosage Recommendations in Adults

Considerations in Determining KALETRA Once Daily vs. Twice Daily Dosing Regimen:

- KALETRA can be given as once daily or twice daily dosing regimen in patients with less than three lopinavir resistance-associated substitutions.
- KALETRA must be given as twice daily dosing regimen in patients with three or more resistance-associated substitutions.
- Table 1 includes the recommended once daily dosing regimen and Tables 2 and 3 include the recommended twice daily dosing regimen.

KALETRA 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, L24I, 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 pregnant women *[see Dosage and Administration (2.4), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

The dose of KALETRA must be increased when administered in combination with efavirenz, nevirapine or nelfinavir.

Table 3 outlines the dosage recommendations for twice daily dosing when KALETRA is taken in combination with efavirenz, nevirapine or nelfinavir.

Table 1. Recommended Dosage in Adults- KALETRA Once Daily Regimen

KALETRA 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 - KALETRA Twice Daily Regimen

KALETRA 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

Table 3. Recommended Dosage in Adults - KALETRA Twice Daily Regimen in Combination with Efavirenz, Nevirapine, or Nelfinavir

KALETRA 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

2.3 Dosage Recommendations in Pediatric Patients

KALETRA tablets and oral solution should not be administered once daily in pediatric patients < 18 years of age. The dose of the oral solution should be administered using a calibrated dosing syringe.

Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a KALETRA tablet, the KALETRA oral solution formulation should be prescribed.

KALETRA 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 *[see Warnings and Precautions (5.2)]*.

KALETRA oral solution contains 42.4% (v/v) alcohol and 15.3% (w/v) propylene glycol. Special attention should be given to accurate calculation of the dosage of KALETRA, 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 children. Total amounts of alcohol 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 KALETRA 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:

$$\text{* BSA } (m^2) = \sqrt{\frac{\text{Ht (Cm)} \times \text{Wt (kg)}}{3600}}$$

The KALETRA dose can be calculated based on weight or BSA:

Based on Weight:

Patient Weight (kg) × Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)

Based on BSA:

Patient BSA (m^2) × Prescribed lopinavir dose (mg/m^2) = Administered lopinavir dose (mg)

If KALETRA oral solution is used, the volume (mL) of KALETRA solution can be determined as follows:

Volume of KALETRA solution (mL) = Administered lopinavir dose (mg) ÷ 80 (mg/mL)

Dosage Recommendation in Pediatric Patients 14 Days to 6 Months:

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution is 16/4 mg/kg or 300/75 mg/m^2 twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area. Table 4 summarizes the recommended daily dosing regimen for pediatric patients 14 days to 6 months.

It is recommended that KALETRA not be administered in combination with efavirenz, nevirapine, or nelfinavir in patients < 6 months of age.

Table 4. Recommended KALETRA Oral Daily Dosage in Pediatric Patients 14 days to 6 months

Patient Age	Based on Weight (mg/kg)	Based on BSA (mg/m^2)	Frequency
14 days to 6 months	16/4	300/75	Given twice daily

Dosage Recommendation in Pediatric Patients > 6 Months to < 18 Years:

Without Concomitant Efavirenz, Nevirapine, or Nelfinavir

Dosing recommendations using oral solution

In children > 6 months to < 18 years of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution without concomitant efavirenz, nevirapine, or nelfinavir is 230/57.5 mg/m^2 given twice daily, not to exceed the recommended adult dose (400/100 mg [5 mL] twice daily). If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for

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