

NEW DRUG UPDATE

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Kaletra® (ABT-378, lopinavir/ritonavir)

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Introduction:

Kaletra® (lopinavir, [loe-PIN-a-veer] / ritonavir, [ri-TOE-na-veer]) is a new antiviral that was approved by the FDA in September 2000 for the treatment of HIV infection. It is the first fixed-dose combination of protease inhibitors. Ritonavir in the co-formulated product inhibits the metabolism of lopinavir, resulting in increased lopinavir concentrations and enhanced activity against resistant strains of HIV. The antiretroviral activity of the mixed product is due to lopinavir. Lopinavir/ritonavir is marketed for use with other HIV drugs in adults and children greater than six months of age. Lopinavir is a new drug available only in this combination, while ritonavir (Norvir®) is often used with other protease inhibitors to raise their plasma concentrations.

Therapeutic Recommendation:

LOPINAVIR/RITONAVIR IS ONE OF SEVERAL PROTEASE INHIBITORS AVAILABLE ON THE MARKET, TO BE USED IN COMBINATION WITH OTHER HIV MEDICATIONS AS PART OF A HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMEN. IT IS DIFFERENT FROM OTHER PROTEASE INHIBITORS CURRENTLY AVAILABLE IN THAT IT IS THE ONLY FIXED-DOSE COMBINATION OF TWO PROTEASE INHIBITORS AND APPEARS TO BE ACTIVE AGAINST SOME STRAINS OF HIV THAT HAVE BECOME RESISTANT TO OTHER PROTEASE INHIBITORS. LOPINAVIR/RITONAVIR MAY BE OF PARTICULAR BENEFIT IN PATIENTS WHO HAVE FAILED OTHER REGIMENS.

Dosing and Administration:

Lopinavir/ritonavir is available as a soft gelatin capsule containing 133.3/33.3 mg of lopinavir and ritonavir, respectively, or as an oral solution containing 80/20 mg of lopinavir and ritonavir, respectively. The recommended adult dosage is three capsules or five milliliters of solution twice daily with food. A dose increase to 533/133 mg (four capsules or 6.5 ml) twice daily taken with food should be considered when efavirenz (Sustiva®) or nevirapine (Viramune®) is concomitantly prescribed, particularly in treatment-experienced patients where reduced susceptibility to lopinavir is suspected. Dosing in infants and children less than 12 years varies according to weight.

Cost Comparison:

Medication/Dose	Cost**		
	Drug Emporium	Kroger	Rite Aid
Kaletra® (lopinavir/ritonavir) 400/100 mg (3 capsules) BID	700.00	770.99	649.00
Viracept® (nelfinavir) 1250 mg (5 tablets) BID	646.69	796.09	640.00
Crixivan® (indinavir) 800 mg (2 capsules) TID	442.76	572.69	425.00
Fortovase® (saquinavir soft-gel) 1200 mg (6 capsules) TID	642.13	760.60	613.00
Norvir® (ritonavir) 600 mg (6 capsules) BID	708.52	761.29	690.00
Agenerase® (amprenavir) 1200 mg (8 capsules) BID	651.89	758.59	669.00

** Cost represents price to patients for a 30-day supply of medication at average doses used

**Inside
This
Issue:**

- ▶ Kaletra® (lopinavir/ritonavir)
- ▶ Mobic® (meloxicam)

Warnings:

- **Drug Interaction ALERT:** Many drugs should not be taken with lopinavir/ritonavir (see Contraindications and Drug Interactions).
- **Pancreatitis:** Pancreatitis has been observed with lopinavir/ritonavir therapy, *including some fatalities*. Although a causal relationship has not been established, the presence of marked triglyceride elevation is a risk factor for the development of pancreatitis. It should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (elevated serum amylase or lipase) suggestive of pancreatitis should occur.
- **Diabetes Mellitus/Hyperglycemia:** New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have all been reported in post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy.

Precautions:

- **Hepatic Insufficiency:** Lopinavir/ritonavir is principally eliminated through the liver; therefore patients with pre-existing hepatic impairment, prior Hepatitis B or C infection, or prior elevated hepatic transaminases may be at risk for elevated lopinavir concentrations and further increases in transaminase levels.
- **Fat Redistribution:** Redistribution of body fat including central adiposity, peripheral wasting, dorsocervical fat enlargement (“buffalo hump”), and breast enlargement has been observed in patients on antiretroviral therapy. The precise mechanism is unknown and has been seen across classes of HIV medications.

- **Hemophilia:** There have been reports of increased bleeding in patients with hemophilia type A and B treated with protease inhibitors. In most cases, therapy with protease inhibitors was continued or reintroduced.
- **Lipid Elevations:** Treatment with lopinavir/ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. These should be determined at baseline and periodically while on treatment. Lipid abnormalities should be managed as clinically appropriate.

Contraindications:

Lopinavir/ritonavir is contraindicated in patients with hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of lopinavir/ritonavir is contraindicated with drugs that are highly metabolized through cytochrome 3A or 2D6 and for which elevated concentrations are associated with serious or life-threatening events. These drugs include:

<u>Drug Class</u>	<u>Contraindicated Drug within Class</u>
Antiarrhythmics	Flecainide (Tambocor) (arrhythmias) Propafenone (Rythmol) (arrhythmias)
Antihistamines	Astemizole (Hismanal) (arrhythmias) Terfenadine (Seldane) (arrhythmias)
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine (ergot toxicity)
GI Motility Agents	Cisapride (Propulsid) (arrhythmias)
Neuroleptics	Pimozide (Orap) (arrhythmias)
Sedative/Hypnotics	Midazolam (Versed) (respiratory depression) Triazolam (Halcion) (respiratory depression)

Special populations:

- **Gender, Race and Age**
Lopinavir pharmacokinetics in the elderly have not been determined. No gender or race related differences in the adult population have been observed.
- **Renal Disease**
Lopinavir pharmacokinetics have not



...A Primary Care Physician's Guide to Newly Released Medications...

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been studied in patients with renal insufficiency; however, since the majority of lopinavir's elimination is through the liver, a decrease in clearance in patients with renal insufficiency is not expected.

- **Hepatic Disease**

Lopinavir is primarily metabolized and eliminated by the liver. Although it has not been studied extensively in patients with hepatic failure, lopinavir concentrations may be increased in these individuals

- **Pediatrics**

Lopinavir has been studied in the pediatric population and is approved for use in children > 6 months of age. The adverse effect profile seen in children between 6 months and 12 years is similar to that for adults.

- **Pregnancy**

Pregnancy Category C. No treatment-related malformations have been observed in pregnant rats or rabbits given lopinavir/ritonavir. Embryonic and fetal developmental toxicities (decreased fetal viability, decreased fetal weight, increased incidence of skeletal variations, etc) were seen in rats but not rabbits given maternally toxic dosages. There are, however, no well controlled studies in pregnant humans. Lopinavir/ritonavir should be administered only when the clinical benefit is perceived to outweigh the risk.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women receiving antiretroviral therapy (including lopinavir/ritonavir), an Antiretroviral Pregnancy Registry has been established. The number to register a patient is 1-800-258-4263.

- **Lactation**

The Centers for Disease Control (CDC) recommends that HIV-infected mothers NOT breast-feed their infants to avoid the risk of transmitting the virus. Studies in rats have demonstrated that lopinavir/ritonavir is secreted in milk; studies in humans have not been done. To avoid the risk of transmitting the HIV virus to the infant as well as potential adverse reactions to the nursing baby, it is recommended that mothers not breast-feed if they are receiving lopinavir/ritonavir.

Drug Interactions:

- Lopinavir is nearly completely metabolized by cytochrome p450 (CYP) 3A. In addition, lopinavir/ritonavir is an inhibitor of CYP3A and, to a lesser degree, CYP2D6. The presence of ritonavir (a potent enzyme inhibitor of CYP3A) in the co-formulated product inhibits the metabolism of lopinavir and potentially other drugs metabolized through the same pathway.

- Clinically important drug interactions with agents metabolized by the isoenzymes CYP2D6 and CYP3A are possible with coadministration of the lopinavir/ritonavir co-formulation.

- **Drugs CONTRAINDICATED with lopinavir/ritonavir (see Contraindications).**

- **Drugs that should NOT BE COADMINISTERED with lopinavir/ritonavir:**

Drug Class

Drug within Class

HMG-CoA reductase inhibitors	Simvastatin (Zocor) (myopathy) Lovastatin (Mevacor) (myopathy)
Antimycobacterials	Rifampin (loss of virologic response, resistance)
Herbal Products	St. John's Wort (loss of virologic response, resistance)

- Drugs that may have INCREASED plasma concentrations when given concurrently:

Drug Class

Drug within Class

Erectile dysfunction	Sildenafil (Viagra)
Antibacterials	Clarithromycin (Biaxin)
Calcium channel blockers	Nifedipine (Procardia)
Antimycobacterials	Rifabutin (Mycobutin)

- Drugs that may DECREASE lopinavir/ritonavir plasma concentrations:

Drug Class

Drug within Class

Anticonvulsants	Phenytoin (Dilantin) Phenobarbital Carbamazepine (Tegretol)
Steroids	Dexamethasone (Decadron)
Antiretrovirals	Efavirenz (Sustiva) Nevirapine (Viramune)

Common Adverse Effects:

Lopinavir/ritonavir is generally well tolerated. The most common adverse effects have been diarrhea, nausea, headache and fatigue. Like all other protease inhibitors, hyperlipidemia, hyperglycemia, increased hepatic transaminases and altered body fat distribution have been reported. Fatal pancreatitis has occurred rarely.

Pharmacology:

Mechanism of Action: Lopinavir inhibits the HIV protease enzyme. This inhibition prevents protein cleavage, resulting in the production of immature, non-infectious viral particles.

Absorption/Distribution: The absolute bioavailability of lopinavir/ritonavir in humans has not been established. Under non-fasting conditions, the bioavailability of the capsules and the oral solution is similar; under fasting conditions, bioavailability of the capsules is 22% higher. Administration of capsules and oral solution given with food increases area under the curve (AUC) of lopinavir by 50% and 80%, respectively. Lopinavir is approximately 98% bound to plasma proteins.

Metabolism/Elimination: Lopinavir is extensively metabolized by the hepatic cytochrome p450 system, almost exclusively by the 3A isoenzyme. Ritonavir is a potent CYP3A4 inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma concentrations of lopinavir. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in urine. The half-life of lopinavir appears to be 5-6 hours.

Patient Information:

1. Lopinavir/ritonavir does not cure HIV infection or AIDS, nor does it reduce the risk of passing HIV to others through sex or blood contamination. Continue to practice safe sex and do not share or use dirty needles.
2. You must take this medication as part of antiretroviral regimen; it should not generally be used by itself to treat HIV infection. You must take it every day exactly as it is prescribed. Do not change your dose or stop taking it without first talking to your doctor. When your supply of medication starts to run low, get more from the pharmacy. This is extremely important as the amount of HIV virus in your body can increase even if the drug is stopped for a short time. The virus may develop resistance and become harder to treat.
3. Take lopinavir/ritonavir twice daily with food to help it work better.
4. Let your doctors and pharmacists know about all other medications (both prescription and nonprescription) that you are taking.
5. Medicines you should not take with lopinavir/ritonavir:
The following medicines can cause serious problems or death if taken with lopinavir/ritonavir:
 - Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafegot, Migranal, D.H.E. 45
 - Halcion (triazolam)
 - Hismanal (astemizole)
 - Orap (pimozide)
 - Propulsid (cisapride)

- Rythmol (propafenone)
- Seldane (terfenadine)
- Tambocor (flecainide)
- Versed (midazolam)

Do not take lopinavir/ritonavir with rifampin (Rimactane, Rifadin, Rifater, or Rifamate) or St. John's Wort. These may lower the amount of lopinavir/ritonavir in the blood and make it less effective.

Do not take lopinavir/ritonavir with the cholesterol-lowering drugs Mevacor (lovastatin) or Zocor (simvastatin) because of possible serious reactions.

References:

1. Lopinavir/ritonavir: a protease-inhibitor combination. *The Medical Letter* 2001; 43(1095):1-2.
2. Tashima KT, Flanigan TP. Antiretroviral therapy in the year 2000. *Infect Dis Clin N Amer* 2000;14(4):1-17.
3. Kaletra® prescribing information. Abbott Laboratories, North Chicago, IL, September 2000.

Mobic® (meloxicam)

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Introduction:

Mobic® (meloxicam [mel-OKS-i-kam]) is a nonsteroidal anti-inflammatory drug (NSAID), which inhibits the enzyme cyclooxygenase. Meloxicam has anti-inflammatory, antipyretic, and analgesic properties. This product was FDA approved on April 14, 2000 for relief of signs and symptoms of osteoarthritis.

Therapeutic Recommendation:

THE ANTI-INFLAMMATORY EFFECT OF MELOXICAM IS DUE TO INHIBITION OF THE ENZYME CYCLOOXYGENASE (COX). THERE ARE TWO ISOFORMS OF THIS ENZYME. COX-1 PROTECTS THE GASTRIC MUCOSA, WHILE COX-2 IS ASSOCIATED WITH INFLAMMATION. OLDER NSAIDS BLOCK BOTH ISOFORMS, WHILE SOME OF THE NEWER NSAIDS ARE SELECTIVE FOR COX-2 INHIBITION. MELOXICAM HAS BEEN AVAILABLE IN EUROPE FOR MANY YEARS. THIS AGENT HAS BEEN FOUND AS EFFECTIVE AS DICLOFENAC AND PIROXICAM IN TREATING OSTEOARTHRITIS. MELOXICAM SHOWS SOME COX-2 SELECTIVITY IN VITRO. BECAUSE MELOXICAM INHIBITS COX-2 MORE THAN COX-1 IN VITRO, THE INCIDENCE OF GASTROINTESTINAL ADVERSE EFFECTS WITH THIS AGENT MAY BE LOWER THAN THAT WITH OLDER NSAIDS.

MELOXICAM IS LESS EXPENSIVE THAN COX-2 SPECIFIC INHIBITORS CELECOXIB AND ROFECOXIB. HOWEVER, MELOXICAM IS NOT A COX-2 SPECIFIC INHIBITOR.

Dosing and Administration:

For the treatment of osteoarthritis, the recommended starting and maintenance dose of meloxicam is 7.5 mg once daily. Some patients may receive benefit by increasing the dose to 15 mg once daily. The maximum recommended daily dose is 15 mg.

Cost Comparison:

Medication/Dose	Cost**		
	<u>Drug Emporium</u>	<u>K-Mart</u>	<u>Rite Aid</u>
Mobic® (meloxicam) 7.5 mg QD	66.34	65.95	66.98
Feldene® (piroxicam) 20 mg QD	*85.92 (23.42)	*93.97 (17.49)	*119.99 (28.98)
Voltaren® (diclofenac) XR 100 mg QD	95.46	*103.97 (88.97)	*126.69 (78.69)
Relafen® (nabumetone) 500 mg 2 tabs QD	79.52	81.00	101.98

**Cost to patient for a 30-day supply at usual dosage for osteoarthritis.

*Brand (Generic)

Precautions:

Contraindications:

Meloxicam is contraindicated in patients with a known hypersensitivity to meloxicam or any of the inactive ingredients contained in the product. It is also contraindicated in patients, who after taking aspirin or other NSAIDs, experienced asthma, urticaria, or allergic-type reactions. Anaphylactic like reactions to NSAIDs have been reported in these patients.

Special populations:

- Risk of GI bleeding, perforation, and ulceration: Minor and serious gastrointestinal problems such as dyspepsia, bleeding, perforation, ulceration, and inflammation may occur at any time during meloxicam treatment. One percent of patients treated for 3-6 months experienced bleeding, perforation, or ulceration, whereas 2-4% experienced these events after being treated for 1 year. Therefore, the likelihood of developing a GI event increases throughout the course of therapy. The lowest effective dose should be used over the shortest period of time possible to minimize the risk of GI adverse events. Patients with a history of peptic ulcer disease and GI bleeding are at an increased risk (10x) of developing GI problems.
- Hepatic impairment: Liver enzymes may increase in patients being treated with meloxicam. Patients taking meloxicam who develop signs and/or symptoms of liver dysfunction should be evaluated. The medication

should be discontinued if the signs and symptoms are consistent with liver disease or if systemic manifestations, such as rash, occur.

- Renal impairment: Metabolites of meloxicam are renally eliminated. There is no need for dosage adjustment in patients with mild to moderate renal impairment (creatinine clearance >15 ml/min). However, use of meloxicam in patients with severe renal failure is not recommended.
- Pediatric: Safety and efficacy of meloxicam has not been established in patients less than 18 years of age.
- Geriatric: Age appears to increase the possibility of developing adverse events with NSAIDs. The risk of serious ulcer disease is increased in patients greater than 65 years of age, especially when using higher doses. Caution should be used when treating elderly patients with meloxicam.
- Pregnancy: Meloxicam is considered pregnancy category C. Increased length of delivery, increased incidence of stillbirths, and delayed parturition was observed in rats receiving 0.5 fold the human dose. An oral dose given to rats up to approximately 2.2 fold the human dose was not teratogenic. Meloxicam does cross the placental barrier. Since no adequate or well-controlled human trials exist, meloxicam should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Meloxicam should not be taken in the third trimester of pregnancy as no human studies have been conducted to determine the effect of meloxicam on the closure of the ductus arteriosus.
- Lactation: Meloxicam is excreted into the milk of lactating rats; however, the agent's excretion into human milk has not been studied. Nursing infants could potentially experience serious adverse reactions. Patients who are breast-feeding should not use meloxicam.
- Congestive heart failure, fluid retention, and hypertension: Patients taking meloxicam, as with other nonsteroidal anti-inflammatory agents, may experience edema and fluid retention. Caution is advised when using meloxicam in patients with heart failure, fluid retention, or hypertension.
- Asthma: Patients with asthma may have aspirin sensitive asthma. These patients may experience severe and possibly fatal bronchospasm when administered aspirin. In these patients, cross reactivity between aspirin and other NSAIDs has been reported. Meloxicam should not be used in patients with aspirin sensitive asthma and should be used with caution in patients with pre-existing asthma.

Drug - Drug Interactions:

- No drug interactions were found between meloxicam and concomitant administration of cimetidine, digoxin, furosemide, or methotrexate.
- Cholestyramine: Pretreatment for four days with cholestyramine increased meloxicam clearance by 50%. Decreases in half-life ($t_{1/2}$) and area under the curve (AUC) of meloxicam were also observed.
- ACE Inhibitors: Meloxicam may decrease the antihypertensive effect of ACE Inhibitors.
- Lithium: Lithium concentrations and AUC were increased in patients receiving meloxicam.
- Warfarin: Meloxicam was not found to alter the pharmacokinetics or the average prothrombin time of warfarin. However, one patient showed an increase in INR when taking warfarin with meloxicam. Caution should be used when administering meloxicam with warfarin.

Common Adverse Drug Reactions:

Gastrointestinal effects including dyspepsia and diarrhea were the most frequently reported adverse effects among patients treated with meloxicam in clinical trials. Daily dose of meloxicam should not exceed 15 mg because higher doses (chronic daily dose of 30 mg) have been associated with an increased risk of serious GI adverse effects.

Pharmacology:

Mechanism of Action: Meloxicam is a nonsteroidal anti-inflammatory drug that has anti-inflammatory, antipyretic, and analgesic properties. Meloxicam inhibits the enzyme cyclooxygenase (COX), which is needed for the production of thromboxanes and prostaglandins. Meloxicam shows some COX-2 selectivity and inhibits COX-2 more than COX-1 in vitro. However, meloxicam is not considered a COX-2 specific inhibitor.

Absorption/Distribution: The bioavailability of meloxicam is 89%. Peak concentrations are reached at 4-5 hours. Absorption of meloxicam is not greatly affected by food.

Metabolism/Excretion: Meloxicam is metabolized in the liver by the cytochrome P450 2C9 isoenzyme primarily, and also by the cytochrome P450 3A4 isoenzyme. The half-life ($t_{1/2}$) of meloxicam is 15-20 hours. Metabolites are excreted in the urine (50%) and in the feces (50%).

Patient Information:

1. Inform your doctors if you experience signs or symptoms of gastrointestinal bleeding or ulceration (such as stomach pain, nausea, vomiting, blood in stool).
2. Notify your doctors if you experience rash, weight gain, or swelling while taking meloxicam.
3. Stop meloxicam treatment and seek medical attention immediately if you experience stomach pain on the right side, "flu-like" symptoms, sluggishness, fatigue, nausea, itching, and jaundice (or yellowing of skin and eyes), as these are warning signs and symptoms of liver impairment.
4. Seek emergency medical attention if, at any time during meloxicam treatment, you develop shortness of breath and/or swelling of your airways (anaphylactoid reaction).
5. Use of meloxicam should be avoided during the third trimester of pregnancy and while breast-feeding.

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