

# NEW DRUG UPDATE

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## Ranexa® (ranolazine)

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### Introduction

Ranexa® (ranolazine [ra-NOE-la-zeen] extended release tablet) was approved by the FDA on January 27, 2006. The FDA indication for ranolazine is chronic stable angina. The medication should be reserved for patients who have not achieved desired response from other antianginal medications, due to the possibility of QTc prolongation.

### Therapeutic Recommendation

Ranolazine is an antianginal medication indicated for chronic stable angina patients who have not reached desired symptom control while taking standard anti-anginal therapy. The mechanism of ranolazine allows it to decrease oxygen demand without changes in heart rate or blood pressure. In placebo controlled clinical trials, ranolazine has proven to increase exercise time before angina attack both as monotherapy and adjunctive therapy

to standard treatment. The MARISA trial (Monotherapy Assessment of Ranolazine in Stable Angina) demonstrated statistical significance over placebo at one week. Ranolazine increased time to angina and ST depression on treadmill testing. The use of ranolazine with beta-blockers, nitrates, amlodipine, and anti-hypertensive agents is well tolerated and recommended. The CARISA trial (Combination Assessment of Ranolazine In Stable Angina) proved to increase exercise time when used in combination with standard therapy (including atenolol, amlodipine, or diltiazem) when compared to placebo. This trial also demonstrated that twice daily ranolazine dosing can provide additional relief in comparison to once daily dosing. Longer term safety was shown in open label continuation at two years with no difference in survival. The most common adverse effects included constipation, dizziness, nausea, and asthenia. In clinical studies 5/261 patients receiving 1000 mg twice daily experienced syncope and was thought to be due to dose dependent postural hypotension. There was a mean 6-9 msec increase in the QTc interval during ranolazine therapy. Precautions should be taken to avoid QTc interval prolongation and monitor the patient at baseline and periodically thereafter using electrocardiography. QTc prolongation can occur due to drug interactions with diltiazem or verapamil. If calcium channel blockers are used, preference may be given to amlodipine, although the CARISA trial did not report

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increased QTc prolongation with the combination of ranolazine and diltiazem. Ranolazine should be used in patients with chronic stable angina therapy and mild to moderate angina despite optimal therapy in accordance with the ACC-AHA (American College of Cardiology/ American Heart Association) treatment guidelines.

### Dosing and Administration

Ranolazine extended release tablets should be initiated at 500 mg twice daily. The dose may be increased to 1000 mg twice daily if symptoms remain poorly controlled. The maximum dose is 1000 mg twice daily. This dose should not be exceeded due to the risk of QTc prolongation at higher doses. Ranexa® is a 500 mg light orange, film coated, extended release tablet. Ranolazine extended release tablets can be taken with or without meals and should not be crushed, chewed or broken.

### Contraindications

Ranolazine should not be prescribed for patients with a history of QTc prolongation, hepatic impairment, or who currently take medications that prolong the QTc interval or inhibit CYP3A4. Patients that have a hypersensitivity to ranolazine or any ingredient in the formulation should not use ranolazine extended release tablets.

### Warnings

QTc prolongation has been shown to occur with

ranolazine therapy in a dose-related manner. With the dose of 1000 mg twice daily the mean QTc prolongation is 6 msec. Do not use doses over 1000 mg twice daily because the risk of QTc prolongation greatly increases. The clinical significance of this adverse effect is unknown and there is no data to determine what occurs in patients with previous QTc prolongation or on medications that also prolong the QTc interval. Initial and periodic electrocardiography monitoring is recommended.

Mild and moderate hepatic impairment will cause an increase in the plasma concentration of ranolazine. This increase leads to a 3 fold increase in the QTc interval. Therefore, ranolazine extended release tablets are contraindicated in hepatic insufficiency.

Ranolazine treatment has been correlated with an average increase in serum creatinine of 0.1 mg/dL. This increase in serum creatinine occurs rapidly and does not progress further during therapy. With discontinuation of ranolazine the serum creatinine will return to baseline. Patients with severe renal impairment do not experience a greater increase in serum creatinine and BUN does not increase during ranolazine therapy.

This drug has multiple drug-drug interactions that are detailed in the drug interaction section.

Ranolazine should be avoided with inhibitors of CYP3A and CYP 2D6. Dose adjustment of digoxin may be necessary.

Data from a study in mice reported an increase in tumor formation. Ranolazine works under hypoxic conditions and tumors are a hypoxic environment.



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

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### Cost Comparison

Medication/Dose	Cost		
	CVS	Rite Aid	Walmart
Ranexa (ranolazine) 500 mg #60	247.99	257.99	213.78
Toprol XL 50 mg #30	41.69	40.99	29.68
Atenolol 50 mg #30	10.99	10.99	6.48
Isosorbide Mononitrate 60 mg #30	29.59	47.99	29.59
Nitrostat SL 0.4 mg #25/bottle	10.99	9.99	5.32
Nitrodur Patch 0.4 mg/hr #30	47.49	121.99	87.32
Diltiazem 180 mg #30	43.09	47.99	38.68
Norvasc 5 mg #30	64.59	60.99	51.68

\*The use of Ranexa® is not indicated at this time for monotherapy. The consideration to use Ranexa® would be in conjunction with other anti-anginal medications.

### Special Populations

**Pediatrics:** The use of ranolazine in patients under the age of 18 has not been investigated.

**Geriatric:** Patients over the age of 75 experienced a higher incidence of adverse events. The adverse effects experienced at a higher frequency include constipation, nausea, and dizziness. However, efficacy of the drug was equivalent between young and elderly patients.

**Gender:** Efficacy in the female population was not as pronounced as in the male population.

**Renal Impairment:** Ranolazine significantly increases blood pressure in patients with severe renal impairment. Regularly monitor blood pressure in this patient population.

**Hepatic Impairment:** Mild to moderate hepatic impairment is associated with an increase in serum concentrations of ranolazine. This increases the risk of QTc prolongation and ranolazine is contraindicated with hepatic impairment.

**Pregnancy:** Clinical studies to determine safety and efficacy during pregnancy have not been conducted. Ranolazine is FDA approved as pregnancy category C and should not be used during pregnancy unless the treatment of the patient outweighs the potential risk to the fetus.

**Lactation:** Excretion of ranolazine in human milk has not been determined. The health care provider should help the patient to decide to continue breast feeding or continue ranolazine therapy, taking into account the importance of ranolazine therapy in the nursing mother.

### Drug Interactions

The primary metabolic pathway for ranolazine is CYP3A. Inhibitors of the CYP3A pathway should be avoided due to risk of increasing the plasma concentration of ranolazine. Examples of these inhibitors include; ketoconazole, otherazole antifungals, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit or grapefruit juice.

Use of ranolazine at the same time as digoxin may increase digoxin levels by 1.5 fold. During concomitant therapy the digoxin dose may have to

be decreased. Digoxin levels should be monitored closely. Other glycoprotein P (P-gp) substrates may have to be decreased when using ranolazine.

Ritonavir and cyclosporine are P-gp inhibitors and can increase levels of ranolazine as a P-gp substrate. Use caution during co-administration of these agents.

Ranolazine is a CYP2D6 inhibitor and will affect the metabolism of drugs that follow the CYP2D6 pathway. These medications include paroxetine, tricyclic antidepressants and some antipsychotics. Monitor these patients for side effects and consider dosage decreases when used with ranolazine.

A two fold increase in simvastatin plasma concentrations has been reported when ranolazine was added to the patient's medication regimen.

### Adverse Events

During the CARISA and ERICA clinical trials the most commonly occurring adverse events included constipation, nausea, dizziness, and headache. The occurrence of dizziness and syncope was shown to be a dose related effect. Adverse events occurring at an incidence of less than 2 % included palpitations, tinnitus, vertigo, abdominal pain, dry mouth, vomiting, peripheral edema, and dyspnea. Adverse events occurring at a rate less than 0.5 % included bradycardia, hematuria, hypoesthesia, hypotension, orthostatic hypotension, paresthesia, tremor, and blurred vision.

### Pharmacology

**Mechanism of Action:** The mechanism of action is not clearly understood. It is suggested that ranolazine inhibits late sodium currents. This is a novel agent, thought to treat toxic myocardial metabolites to decrease the magnitude of ischemia induced by sodium and calcium overload, improving myocardial function as well as perfusion. Most antianginal agents work to increase oxygen supply or decrease oxygen demand, but ranolazine works to decrease oxidative stress without increasing cardiac work.

**Absorption/Distribution:** Oral bioavailability of ranolazine is 76%. Peak plasma concentration is achieved 2 to 5 hours after dosing. When dosing ranolazine twice daily, steady state is reached after 3 days. Food does not affect the absorption of

ranolazine. Absorption of ranolazine may be increased with P-glycoprotein inhibitors coadministered. Ranolazine is 62% bound to human plasma proteins.

**Metabolism/Excretion:** Ranolazine is metabolized by the liver and intestine. The drug is extensively metabolized by the CYP3A pathway and moderately by the CYP2D6 pathway. The drug is 75% excreted in the urine and 25% excreted in the feces. Only 5% of ranolazine is excreted unchanged in the urine and feces. The activity of the metabolites has not been proven.

### Patient Education

1. Do not crush, chew, or break ranolazine extended release tablets.
2. Ranolazine may be taken without regard to food.
3. Ranolazine will not work during an acute angina attack. Use nitroglycerin if directed for acute anginal attacks.
4. Because of the possible drug interactions and contraindications, it is very important to provide your health care providers with an accurate medication history, including nonprescription medications and supplements.
5. Dizziness and lightheadedness may occur while taking ranolazine. Patients should not operate machinery or partake in activities requiring alertness until they know how they respond to ranolazine.

### References

1. Ranexa® (ranolazine). Product Information. CV Therapeutics, Inc., Palo Alto, CA. January 2006.
2. Gaffney SM. Ranolazine, a novel agent for chronic stable angina. *Pharmacotherapy*. 2006; 26(1): 135-42.
3. Chaitman BR, *et al.*, for the Combination Assessment of Ranolazine in Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic stable angina. *JAMA* 2004; 291: 309-16.
4. Chaitman BR, *et al.* Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. (MARISA) *J Amer Coll Cardiol*. 2004; 43 (8): 1375-82.
5. Suckow MA, *et al.* The anti-ischemia agent ranolazine promotes the development of intestinal tumors in APC (min/+) mice. *Cancer Letters* 2004: 209 165-9.

## Orencia® (abatacept)

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### Introduction

Orencia® [abatacept (ab-a-TA-sept)] is a recombinant human fusion protein that treats rheumatoid arthritis by blocking T-cell activation. Orencia® received FDA approval on December 23, 2005 and is indicated for treating signs and symptoms of rheumatoid arthritis in individuals without an adequate response to disease-modifying antirheumatic drugs (DMARDs).

### Therapeutic Recommendation

**Abatacept is approved to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis (RA), to induce a significant response, to reduce and/or slow structural damage to joints, and to improve physical functionality in those patients who do not respond to DMARDs. One study that lasted six months showed a statistically significant benefit of abatacept over placebo in rates of ACR 20 response (50.4% vs. 19.5%) and a clinically important improvement of at least 0.3 on the Health Assessment Questionnaire (HAQ) disability index. The HAQ is a patient-based assessment that measures quality of life. The ACR 20 response criteria includes a decrease of at least 20% in the number of swollen and tender joints and a 20% improvement in 3 of the following: patient's global assessment of disease activity, patient's assessment of pain, physical function, physician's global assessment of disease activity, and the C-reactive protein level. This study also showed superiority of abatacept over placebo in ACR 50 response (20.3% vs. 3.8%) and ACR 70 response (10.2% vs. 1.5%) after six months of treatment. Abatacept can be used alone or in combination with DMARDs except tumor necrosis factor alpha antagonists. A 12-month study showed that at**

day 60 the number of patients who achieved an ACR 20 response was significantly greater in patients taking abatacept plus methotrexate than those taking placebo plus methotrexate (56.5% vs. 34.5%). This trend continued until month 12 and the response remained statistically significant at day 360 (62.6% vs. 36.1%). This study also showed that abatacept plus methotrexate was superior to placebo plus methotrexate in achieving ACR 50 response (13.9% vs. 5.9%) and ACR 70 response (3.5% vs. 0%) as early as day 30 and benefit continued until the end of the trial in both the ACR 50 response (41.7% vs. 20.2%) and the ACR 70 response (20.9% vs. 7.6%). A multicenter, randomized, double-blind, placebo controlled trial presented at the 2006 American College of Rheumatology meeting compared regimens of methotrexate with abatacept and methotrexate with infliximab. In this study after one year, the abatacept group demonstrated ACR 20, 50, and 70 responses of 72%, 45% and 26% respectively. In comparison, those who were assigned to the infliximab group had ACR 20, 50, 70 scores of 56%, 36%, and 21% respectively. Additionally, serious adverse events and discontinuations of therapy were about 50% less in those receiving the abatacept regimen.

**Dosing and Administration**

Abatacept is available only as an intravenous infusion and dosing is based on a weight range scale. Patients weighing less than 60 kg should receive 500 mg per dose (2 vials), those between 60 kg and 100 kg should receive 750 mg per dose (3 vials), and those weighing greater than 100 kg should receive 1 g per dose (4 vials). This dose should be administered as a 30-minute infusion. Abatacept should be given 2 and 4 weeks after initial administration, then every 4 weeks thereafter. Orencia® is supplied as a lyophilized powder in single-use vials (250 mg of abatacept per vial) and should be reconstituted with 10 ml of sterile water for injection. Reconstitution should only be done using the silicone-free disposable syringe provided with each vial. Using a siliconized syringe will result in the formation of a translucent precipitate. If a siliconized syringe is used, the solution should be discarded immediately. To avoid formation of foam, a gentle swirling technique should be used during reconstitution. After reconstitution, the solution must be further diluted

to 100 ml using normal saline. The final concentration will be approximately 5 mg/ml (500 mg dose), 7.5 mg/ml (750 mg dose), or 10 mg/ml (1 g dose).

**Cost Comparison**

Medication/Dose	Cost		
	<u>CVS</u>	<u>Kmart</u>	<u>RiteAid</u>
Orencia® (abatacept)			
500 mg (2 vials)	1160.99	1147.97	1200.99
750 mg (3 vials)	1722.99	1721.97	1781.99
1000 mg (4 vials)	2285.99	2295.97	2363.99
(This is the price per dose: the normal regimen is 1 dose at week 0, week 2, week 4, then every 4 weeks.)			
Enbrel® (etanercept)			
25 mg	788.99	764.97	773.99
50 mg	1602.99	1529.97	1501.99
(This is the price for a kit containing therapy for 4 weeks)			
Remicade® (infliximab)			
300 mg (3 vials)	2105.99	2112.97	2177.99
400 mg (4 vials)	2796.99	2816.97	2891.99
(This is the price per dose; the normal regimen is 1 dose at week 0, week 2, week 6, then every 8 weeks.)			

**Precautions**

Abatacept may significantly increase risk for developing infection. Therefore, caution should be used in patients with recurrent infections or those at increased risk for infections. Caution is advised in patients with agranulocytosis, asthma, bone marrow suppression/transplant, COPD, corticosteroid therapy, cystic fibrosis, diabetes mellitus, advanced age, emphysema, immunosuppression, current infection, neoplastic disease, respiratory infection, sepsis, smoking, or tuberculosis.

**Special Populations**

Hepatic Impairment: No studies have established dosing guidelines in this population.

Renal Impairment: No studies have established dosing guidelines in this population.

Pediatrics: No clinical trials have studied use of abatacept in patients <18 years old.

Geriatrics: No dosing adjustments are needed, but caution is advised.

Pregnancy: Abatacept is pregnancy category C. No clinical studies have shown safety during pregnancy, so it should only be used if clearly needed.

Lactation: It is unclear if abatacept is excreted in milk or absorbed when ingested, so administration should be avoided while breastfeeding.

### Pharmacology

**Mechanism of Action:** Abatacept binds to CD80 and CD86 and blocks their interaction with CD28 to inhibit the activation of T cells. Activated T cells have been found in the synovium of patients with rheumatoid arthritis, and are suspected to be involved in the pathogenesis of the disease. Abatacept inhibits activation of T cells, production of TNF alpha, production of interferon-gamma, and production of interleukin-2.

**Absorption/Distribution:** Abatacept is administered intravenously. Pharmacokinetic values in RA patients and healthy patients were comparable. With multiple infusions, C<sub>max</sub> and AUC showed proportional increases through the recommended dosage range. Steady state was reached by day 60 in test subjects. The volume of distribution is 0.9 L/kg in healthy subjects and 0.07 L/kg in RA patients.

**Metabolism/Excretion:** Little is known about the metabolism of abatacept. The terminal half-life of this infusion is 13-16 days in both healthy patients and RA patients. Systemic clearance is 0.23 ml/h/kg in healthy patients and 0.22 ml/h/kg in RA pa-

tients. Studies showed a trend toward increased clearance with increasing body weight. Neither age nor gender affected clearance.

### Patient Education

1. Tell your doctor all medications you are currently taking including over-the-counter medications, vitamins, and supplements.
2. Tell your doctor if you have any medical condition that puts you at increased risk for infections or if you smoke.
3. Tell your doctor if you are breast-feeding, pregnant, or plan on becoming pregnant.
4. Tell your doctor if you experience fever, chills, rash, hives, trouble breathing, or swollen face, eyelids, lips, tongue, or throat while on abatacept.
5. You may experience dizziness, headache, nausea/vomiting, or upset stomach while taking abatacept.
6. Abatacept is administered in a hospital or clinic setting; it should not be taken at home or without the supervision of a properly trained health care professional.

### References

1. Orenzia® (abatacept) prescribing information, Bristol-Myers Squibb Company. Princeton, NJ, December 2005.
2. Genovese MC, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor  $\alpha$  inhibition. *NEJM* 2005; 353: 1114-23.
3. Kremer JM, *et al.* Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept. *Arthritis Rheum* 2005; 52: 2263-71.
4. Schiff *et al.* American College of Rheumatology 2006, L43.



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