

## CARVEDILOL – COREG (Smith Kline Beecham)

### INDICATIONS:

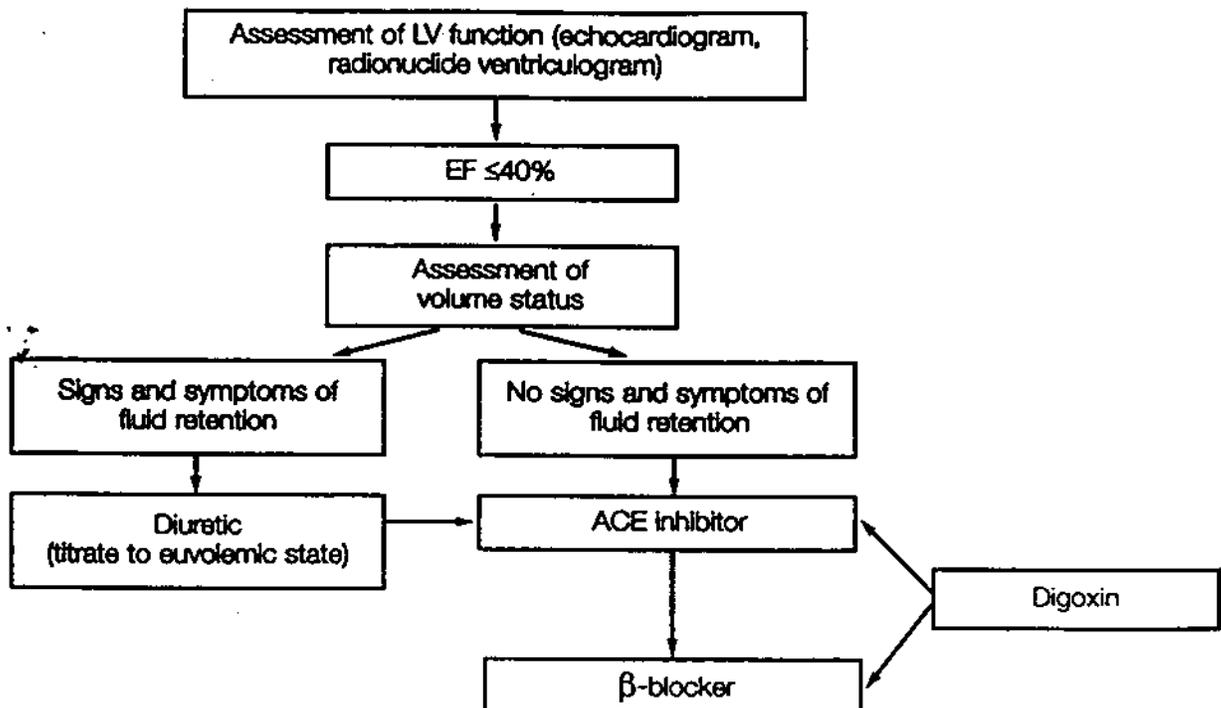
Carvedilol is indicated for treatment of mild to moderate heart failure (NYHA class II or III) of ischemic or cardiomyopathic origin, in conjunction with digitalis, diuretics, and ACEI, to reduce progression of disease as evidenced by CV death, hospitalization, or the need to adjust other heart failure medications. The drug may also be used in patients who are unable to tolerate an ACEI or in patients who are receiving hydralazine and or nitrates.

Carvedilol is also approved for the management of essential hypertension.

Cost \$1.55 per dose all four strengths (3.125mg; 6.25mg; 12.5mg and 25mg)

### CONSENSUS RECOMMENDATIONS FOR THE MANAGEMENT OF CHRONIC HEART FAILURE from the Advisory Council To Improve Outcomes Nationwide in Heart Failure (ACTION HF)

Am J Cardiol 1999;83(2A):1A-38A.



**FIGURE 1.** Approach to the patient with heart failure. Patients should be evaluated in accordance with the recommendations outlined in Table I and should receive the general measures presented in Table III. In particular, left ventricular (LV) function should be evaluated in all patients with heart failure to detect those with systolic dysfunction [ejection fraction (EF)  $\leq 40\%$ ]. Patients with evidence of fluid retention should receive a diuretic until a euvolemic state is achieved (as outlined in Table IV), and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with an angiotensin-converting enzyme (ACE) inhibitor and a  $\beta$  blocker should be initiated and maintained in appropriate patients (as described in Tables V and VI), unless these drugs are not tolerated or their use is contraindicated. Therapy with digoxin may be initiated at any time to reduce symptoms or to slow the ventricular response in patients with rapid atrial fibrillation (as summarized in Table VII). Other agents may be considered in selected patients (as discussed in Tables VIII–XII).

**TABLE IV Use of Diuretics in Heart Failure**

- Diuretics should be prescribed for all patients with symptoms of heart failure who have evidence for or a predisposition to fluid retention, since these drugs are the only reliable means of controlling the fluid retention of heart failure. However, diuretics should not be used alone even if the symptoms of heart failure are well controlled, but should generally be combined with an ACE inhibitor and a  $\beta$  blocker.
- The goal of diuretic therapy is to eliminate symptoms as well as physical signs of fluid retention, as assessed by jugular venous pressures or peripheral edema, or both. If hypotension or azotemia is observed before these goals are achieved, the physician may elect to slow the rapidity of diuresis, but the diuresis should nevertheless be maintained until fluid retention is eliminated, as long as the changes in blood pressure and renal function are mild or moderate in severity and do not produce symptoms.
- The most useful approach to selecting the dose of, and monitoring the response to, diuretic therapy is by measuring body weight, preferably on a daily basis.
- Diuretics may alter the efficacy and toxicity of nearly all the drugs used for the treatment of heart failure. Underdosing of diuretics can lead to fluid retention, which may diminish the response to ACE inhibitors and increase the risk of treatment with  $\beta$  blockers. Overdosing of diuretics can lead to volume depletion, which may increase the likelihood of hypotension with ACE inhibitors and vasodilators and the risk of renal insufficiency with ACE inhibitors and angiotensin II receptor antagonists.
- Diuretic resistance (which accompanies the progression of heart failure) can be overcome (1) by the intravenous administration of diuretics; (2) by the use of  $\geq 2$  diuretics in combination (e.g., furosemide and metolazone); or (3) by the short-term use of drugs that increase renal blood flow (e.g., dopamine and dobutamine). Diuretic resistance may also be caused by concomitant therapy with nonsteroidal anti-inflammatory drugs.

**TABLE V Use of ACE Inhibitors in Heart Failure**

- All patients with heart failure due to left ventricular systolic dysfunction should receive an ACE inhibitor unless they have been shown to be intolerant to or have a contraindication to the use of this class of drugs. In patients with evidence for or a prior history of fluid retention, ACE inhibitors are generally used together with diuretics. ACE inhibitors are also recommended for use in patients with left ventricular systolic dysfunction who have no symptoms of heart failure.
- Patients receiving therapy with an ACE inhibitor should be advised that (1) side effects may occur early in therapy but do not generally prevent long-term use of the drug; (2) symptomatic improvement may not be seen until patients have received treatment for several weeks or months; and (3) ACE inhibitors may reduce the risk of disease progression even if the symptoms of the patient have not responded favorably to treatment.
- ACE inhibitors are indicated for the long-term management of chronic heart failure. These drugs should generally not be used to stabilize acutely ill patients ("rescue" therapy), e.g., those who are in the intensive care unit with refractory heart failure requiring intravenous pressor support.
- Although clinical trials suggest that all ACE inhibitors are likely to exert favorable effects in heart failure, preference should be given to the target doses of the specific ACE inhibitors evaluated in large-scale studies.

**TABLE VI Use of Beta Blockers in Heart Failure**

- All patients with stable NYHA class II or III heart failure due to left ventricular systolic dysfunction should receive a  $\beta$  blocker unless they have a contraindication to its use or have been shown to be unable to tolerate treatment with the drug;  $\beta$  blockers are generally used together with diuretics and ACE inhibitors.
- Patients receiving therapy with a  $\beta$  blocker should be advised that (1) side effects may occur early in therapy but do not generally prevent long-term use of the drug; (2) symptomatic improvement may not be seen until the patient has received treatment for 2-3 months; and (3)  $\beta$  blockade may reduce the risk of disease progression even if the symptoms of the patient have not responded favorably to treatment.
- More data are needed on the effect of  $\beta$  blockers in unstable patients or in patients with current or recent class IV symptoms before the drugs can be recommended for use in such patients.
- Beta blockers are indicated for the long-term management of chronic heart failure. Beta blockers should not be used in acutely ill patients ("rescue" therapy), including those who are in the intensive care unit with refractory heart failure requiring intravenous support.

**TABLE VII Use of Digitalis in Heart Failure**

- Digoxin is recommended to improve the clinical status of patients with heart failure due to left ventricular systolic dysfunction and should be used in conjunction with diuretics, an ACE inhibitor, and a  $\beta$  blocker. The drug is also recommended in patients with heart failure who have rapid atrial fibrillation, even though  $\beta$  blockers may be more effective in controlling the ventricular response during exercise.
- Although some physicians have advocated using serum levels to guide the selection of an appropriate dose of digoxin, there is no evidence to support the validity of such an approach.
- Despite pervasive fears about toxicity, digoxin is well tolerated by most patients with heart failure. Whether long-term therapy with digoxin may exert deleterious cardiovascular effects at doses that are generally considered to be in the therapeutic range remains unknown.

**TABLE VIII** Role of Hydralazine-Nitrate Combination in Heart Failure

- The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of heart failure in patients who have no prior use of ACE inhibitors and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.
- Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors, the combined use of hydralazine and isosorbide dinitrate should be considered as a therapeutic option in such patients, particularly in those who cannot take an ACE inhibitor because of hypotension or renal insufficiency.
- There is little evidence to support the use of nitrates alone or hydralazine alone in the treatment of heart failure.

**TABLE IX** Role of Angiotensin Receptor Blockers and Aldosterone Antagonists in Heart Failure

- There is no persuasive evidence that angiotensin II receptor antagonists are equivalent or superior to ACE inhibitors in the treatment of heart failure. Therefore, angiotensin II receptor antagonists should not be used for the treatment of heart failure in patients who have no prior use of ACE inhibitors and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.
- Because of the lack of conclusive evidence supporting the efficacy of these drugs in heart failure, it is reasonable to prescribe angiotensin II receptor antagonists instead of ACE inhibitors only in patients who are intolerant of ACE inhibitors due to angioedema or intractable cough. Angiotensin II receptor antagonists appear as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia.
- Because spironolactone appears to reduce mortality in patients with current or recent class IV symptoms, use of this drug merits consideration in patients with advanced heart failure.

**TABLE X** Role of Calcium Antagonists in Heart Failure

- Because of the lack of evidence supporting efficacy, calcium antagonists should not be used for the treatment of heart failure. Large-scale trials of newer agents have not provided persuasive evidence that long-term treatment with these drugs can improve the symptoms of heart failure or prolong survival.
- Because of concerns about safety, most calcium antagonists should be avoided in patients with heart failure, even when used for the treatment of angina or hypertension. Of the available agents, clinical trials have provided long-term safety data only for amlodipine and felodipine. There is persuasive evidence that amlodipine does not adversely affect survival.
- The possibility that amlodipine might have a favorable effect on survival in patients with a nonischemic cardiomyopathy requires further study (and confirmation) before such a finding is applied to the care of patients with heart failure.

**TABLE XI** Role of Antiarrhythmic Agents in Heart Failure

- Class I antiarrhythmic agents should not be used in patients with heart failure, except in the treatment of immediately life-threatening ventricular arrhythmias that are refractory to treatment.
- Some class III antiarrhythmic agents (e.g., amiodarone) do not appear to increase the risk of death in patients with chronic heart failure. Such drugs are preferred over class I agents when used for the treatment of atrial arrhythmias in patients with left ventricular dysfunction.
- Given its known toxicity and equivocal evidence for efficacy, amiodarone is not recommended for general use to prevent death (or sudden death) in patients with heart failure already treated with drugs that reduce mortality (e.g., ACE inhibitors and  $\beta$  blockers).
- Physicians should monitor and correct any deficiencies in potassium and magnesium balance, since these may cause atrial and ventricular arrhythmias or alter the efficacy and toxicity of anti-arrhythmic interventions.

**TABLE XII** Role of Outpatient Infusions of Positive Inotropic Agents in Heart Failure

- Because of the lack of data demonstrating efficacy and concerns about toxicity, the use of *intermittent* infusions of positive inotropic therapy (at home, in an outpatient clinic, or in a short-stay unit) cannot be recommended in the treatment of heart failure, even in its advanced stages.
- The long-term use of intravenous positive inotropic therapy may increase the risk of death. It is recognized that such a risk may be worth taking in highly selected patients who have refractory symptoms of heart failure at rest and cannot be weaned from continuous intravenous inotropic support. It is possible that the *continuous* infusion of positive inotropic agents could improve the quality of life in such patients who otherwise would be unable to be discharged from the hospital or maintain clinical stability as an outpatient for more than a few days.

Carvedilol for heart failure: Renewed interest in beta blockers  
 James B. Young, MD, Section Head Heart Failure and Cardiac Transplant  
 Medicine, Dept. Cardiology, Cleveland Clinic  
 Cleveland Clinic Journal of Medicine 1997;64:415-22.

**TABLE 1**

**POTENTIAL BENEFITS  
 OF BETA BLOCKERS  
 IN PATIENTS WITH HEART FAILURE**

- Reduce norepinephrine release by prejunctional beta receptors
- Reduce peripheral vascular resistance  
(with agents having alpha-blocking effects)
- Reduce venomotor tone
- Reduce plasma volume
- Reset carotid baroreceptors
- Attenuate the response to catecholamines during exercise
- Inhibit renin secretion
- Reduce heart rate
- Restore heart-rate variability
- Attenuate potentially malignant ventricular arrhythmias
- Control atrial arrhythmia rate
- Reduce ventricular wall stress
- Ameliorate myocardial ischemia

**TABLE 2**

**PHARMACODYNAMIC PROPERTIES OF BETA BLOCKERS  
 USED IN RANDOMIZED TRIALS IN HEART FAILURE**

Agent	Beta <sub>1</sub> selectivity*	Alpha <sub>1</sub> antagonism	Partial agonist activity	Peripheral vascular resistance
Acebutolol	Modest	None	Modest	Increase or no change
Bisoprolol†	Strong	None	None	Increase or no change
Bucindolol	None	None	Modest	Decrease
Carvedilol	None	Modest	None	Decrease
Labetalol	None	Modest	Modest	Decrease
Metoprolol	Strong	None	None	Increase or no change
Nebivolol†	Modest	None	None	Data not available
Propranolol	None	None	None	Increase

\*Selectivity seen only with low therapeutic doses

†Not clinically available

## EFFECTS OF CARVEDILOL IN CONGESTIVE HEART FAILURE (PLACEBO-CONTROLLED TRIALS)

Study	No. of patients	Follow-up (months)	Effect on ejection fraction	Effect on exercise tolerance	Effect on NYHA classification	Effect on global assessment
Olsen et al <sup>18</sup>	60	4	Increased	No change	Improved	Improved
Metra et al <sup>19</sup>	40	4	Increased	Increased	Improved	Improved
Krum et al <sup>20</sup>	49	3	Increased	Increased	Improved	Improved
US mild CHF <sup>22</sup>	366	12	Increased	Not available	Improved	Improved
PRECISE <sup>23</sup>	278	6	Increased	Increased	Improved	Improved
MOCHA <sup>24</sup>	346	6	Increased	No change	No change	No change
US severe CHF <sup>25</sup>	105	6	Increased	Increased	Improved	Improved
AUS-NZ <sup>26</sup>	415	20	Increased	No change	No change	No change

US mild CHF=United States Carvedilol Heart Failure Program mild-heart-failure study

PRECISE = Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (United States Carvedilol Heart Failure Program moderate-heart-failure study)

MOCHA = Multicenter Oral Carvedilol Heart Failure Assessment (United States Carvedilol Heart Failure Program dose-ranging study)

US severe CHF = United States Carvedilol Heart Failure Program severe-heart-failure study

AUS-NZ = Australia-New Zealand Carvedilol Heart Failure trial

### HOW TO USE CARVEDILOL IN HEART FAILURE\*

#### Patient selection

Mild to moderate heart failure

Already receiving angiotensin-converting enzyme inhibitors, a diuretic and digoxin

Not recommended in patients hospitalized for decompensated heart failure, or who have significant hypotension or pulmonary congestion

#### Dosage

Start with 3.125 mg twice a day for 2 weeks

Observe the patient for side effects 1 to 2 hours after initial dose and each dose increase or have the patient take these doses at bedtime

If first dose is tolerated well, increase to 6.25 mg twice a day after 2 weeks

Double the dose every 1–2 weeks until target reached

25 mg twice a day in patients weighing 85 kg or less  
or 50 mg twice a day in patients weighing more than 85 kg

Tell the patient to take carvedilol with meals

#### Side effects during upward titration

Vasodilator effects (dizziness or light-headedness)

Give the drug with food

Give drug 2 hours before other agents

Consider reducing diuretic or vasodilator doses temporarily

Reduce carvedilol dose

May require no attention, as symptoms are often self-limiting

Worsening heart failure (edema, weight gain, dyspnea)

Intensify salt restriction

Increase diuretic dose

Reduce carvedilol dose

Significant bradycardia (consistently < 60–65/minute with symptoms)

Reduce carvedilol dose

Monitor digoxin levels

Reduce digoxin dose

**Carvedilol vs. Placebo in Patients with Chronic Heart Failure (EF ≤ 0.35) Already on Digoxin, Diuretics, and ACEI - 6 Month Results (12 months for patients with mild CHF) (NEJM 1996;334:1349-55)**

Event	Placebo (%) (n = 398)	Carvedilol (%) (n = 696)	RRR	ARR	NNT
Total Mortality	7.8%	3.2%	65%	4.6%	22
CV Hospitalization	19.6%	14.1%	27%	5.5%	18
Hospitalization or Death	24.6%	15.8%	38%	9.2%	11

**Table 1. Pretreatment Characteristics of Patients in the Study\***

Characteristic	Placebo (N = 398)	Carvedilol (N = 696)
Age (yr)	58.1 ± 12.3	57.9 ± 12.2
Sex (M/F)	304/94	534/162
New York Heart Assoc. Class		
II	208	374
III	177	303
IV	13	19
Cause of Heart Failure†		
Coronary Artery Disease	189	332
Nonischemic dilated cardiomyopathy	208	362
Left ventricular ejection fraction	0.22 ± 0.07	0.23 ± 0.07
Six-minute walk (m)	386 ± 96	390 ± 90
Systolic blood pressure (mm Hg)	115 ± 17	116 ± 17
Diastolic blood pressure (mm Hg)	73 ± 11	72 ± 10
Heart rate (beats/min)	83 ± 12	84 ± 12
Medication (% of patients)		
Digitalis	90	91
Loop Diuretic	95	95
ACE inhibitor	95	95
Direct-acting vasodilator	32	32

\* Plus-minus values are means ± SD. ACE denotes angiotensin-converting enzyme.  
 † The cause of heart failure was not recorded for one patient in the placebo group and two in the carvedilol group.

**MERIT –HF (Metoprolol CR/XL Randomized Intervention Trial in Heart Failure)**

**Preliminary data**

3991 patients randomized (94% Caucasian), mean age 64 (77% male); mean EF 0.28; NYHA class II-41%, III-55%, IV-4%; ischemic origin 62%; previous MI 47%; hypertension 44%; Diabetes 25%; concurrent medications- ACEI 89%, ARBs 7%, diuretics 90%, digitalis 70%, ASA 50% and Lipid lowering agents 29%.

Randomized to placebo or metoprolol CR/XL ( first two weeks 12.5 –25mg/day, week 3-4 - 50mg/day, weeks 5-6 – 100mg/day, and week 7-8 – 200mg/day). Note that patients with NYHA class III/IV were started on 12.5mg/day. At 3 months the mean dose was 163mg/day with 64% of patients on 200mg/day.

Primary end points were total mortality, all cause mortality and all cause hospitalization. The Independent Safety Committee stopped the trial prematurely Oct. 31, 1998 because of a 35% reduction in total mortality. All patients were subsequently offered open label metoprolol CR/XL. The results are scheduled to be presented at ACC in March 1999.

**CIBIS-II Preliminary Data to determine the impact of bisoprolol in heart failure on all cause mortality.**

Inclusion criteria- ambulatory patients with NYHA class III/IV who are stable on ACEI and diuretics age 18-80 and with LVEF less than or equal to 35%. 2647 patients were recruited in the randomized double-blind European multicenter trial and followed for 2 years. Patients were 80% male, 61% were less than 65 years of age; 58-59% had ischemic failure with 40-41% non-ischemic; NYHA class III – 83-84% vs. 16-17% were class IV. Patients were very slowly titrated over 6 months from 1.25mg to 10mg/day of bisoprolol.

All cause mortality was 17.3% in the placebo group vs. 11.8% in the bisoprolol group. RRR 32% ( $p=0.00005$ ). Average follow-up 1.4 years. Sudden death was reduced by 45% -primary reason for reduction in all cause mortality. Hospitalizations for heart failure were reduced by 30%. Withdrawal rates were 15% in both groups.

**RALOXIFENE - Evista® by Eli Lilly and Company - 1S**

**CLINICAL PHARMACOLOGY:** Raloxifene is a selective estrogen receptor modulator (SERM). A nonsteroidal benzothiophene antiestrogen with partial estrogen agonist effects, it binds to the estrogen receptor with high affinity. Raloxifene acts as an antiestrogen in breast and uterine tissue and as an estrogen agonist in bone and lipid metabolism. It reduces bone resorption, decreases overall bone turnover and reduces serum cholesterol, without the effects on the uterus and breast tissue that are observed with estrogen. Compared to tamoxifen, it is a weaker estrogen agonist on reproductive tissues and a more potent agonist on the skeleton. It has been shown to preserve bone mass and bone strength in ovariectomized animals, inhibit the hypertrophy of the uterus in response to estrogen and reduce serum cholesterol levels. In animal models, it has produced effects similar to estrogen on weight gain, serum cholesterol, bone mineral density and cortical and cancellous bone growth and turnover, although effects on bone formation were of a lesser magnitude. Anti bone resorptive effects comparable to estrogen, tamoxifen and alendronate have been observed in ovariectomized rats.

**PHARMACOKINETICS:** Raloxifene is 60% absorbed following oral administration; however, it undergoes extensive presystemic glucuronide conjugation, resulting in an absolute bioavailability of 2%. Administration with a high-fat meal increases absorption (28% increases in peak plasma concentrations and 16% increase in the AUC), but not to a clinically important extent. Therefore, raloxifene can be administered without regard to meals. Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins, primarily albumin and alpha<sub>1</sub>-acid glycoprotein but not to sex steroid binding globulin.

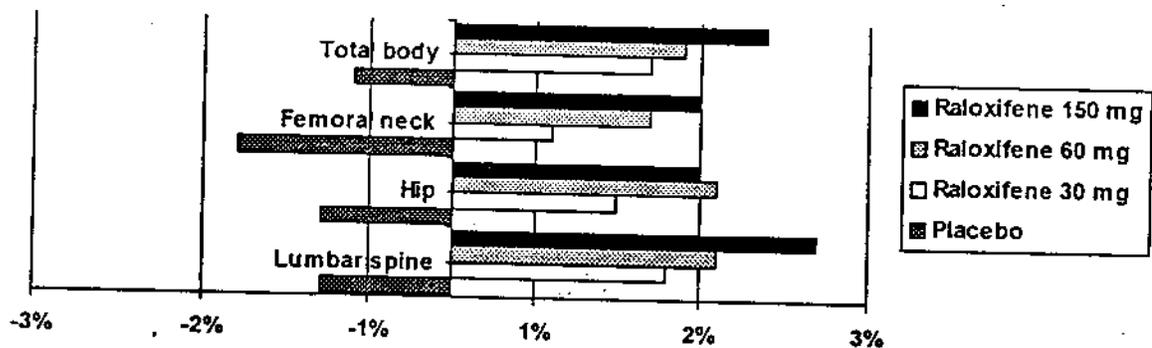
Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates. Raloxifene and the conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, prolonging the plasma elimination half-life to 27.7 hours after oral dosing. Raloxifene is excreted primarily in the feces, with less than 0.2% of the dose excreted unchanged in the urine and less than 6% of the dose excreted in the urine as glucuronide conjugates.

Raloxifene pharmacokinetics were not altered in women with mild-to-moderate renal dysfunction (estimated creatinine clearance as low as 23 mL/min). In patients with cirrhosis and total serum bilirubin ranging from 0.6 to 2 mg/dL, plasma raloxifene concentrations were 2.5 times higher than in controls and correlated with bilirubin concentrations. Further studies have not been performed in patients with hepatic dysfunction.

**COMPARATIVE EFFICACY:** The effects of raloxifene on bone mineral density, serum cholesterol and uterine endometrium in postmenopausal women were described in the interim results of a double-blind clinical trial enrolling 601 postmenopausal women in Europe. These women were treated with raloxifene 30,

60 or 150 mg once daily or placebo for 24 months. In addition to raloxifene or placebo, all women also received a daily supplement of calcium 400 to 600 mg. Women enrolled in the study were 45 to 60 years of age, were within 2 to 8 years of menopause and had a lumbar-spine bone mineral density between 2.5 SD below and 2 SD above the mean value for normal premenopausal women. Exclusion criteria were extensive, with patients excluded if they had a history of estrogen-dependent tumors; had cancer within the last 5 years; had taken androgen, estrogen, calcitonin or glucocorticoids within the previous 6 months; had ever taken a bisphosphonate or fluoride (except dental prophylaxis); were taking antiseizure medications; were taking pharmacologic doses of vitamin D or lipid-lowering drugs; had a history of thromboembolic disorders, diabetes mellitus or other endocrine disorders requiring therapy (except thyroid hormone replacement); had abnormal renal function or hepatic function; had serious postmenopausal symptoms or abnormal uterine bleeding; had consumed an excess of alcohol or abused drugs. The effects on hip and lumbar spine bone mineral density with raloxifene in this study, although greater than with placebo, were less than those previously reported with estrogens or alendronate.

Figure 1: Bone Mineral Density (mean percent change from baseline)

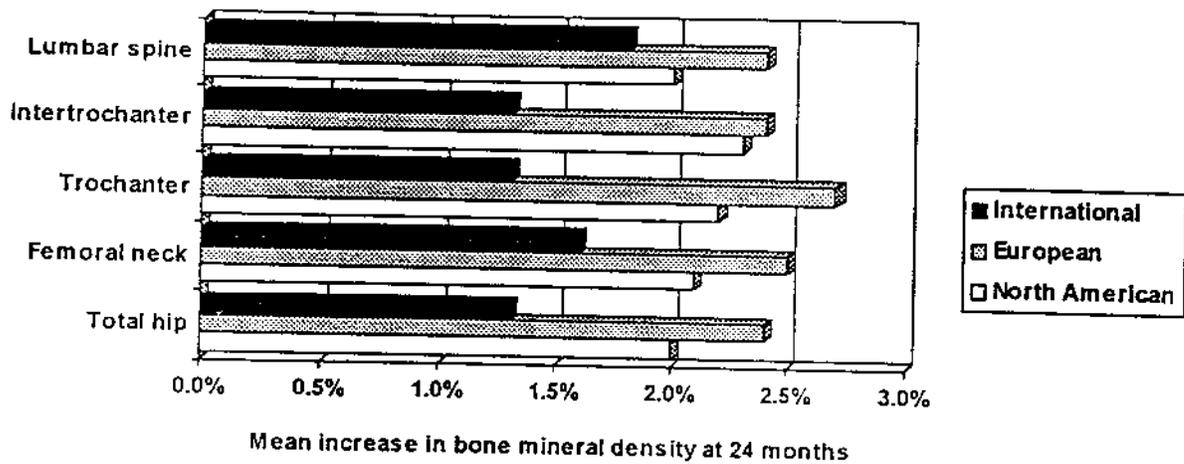


Mean percent change from baseline

\* All values are significantly different from those for placebo ( $p < 0.03$ ).

In addition to this large study, data from two other large, 24-month, placebo controlled, double-blind studies are included in the product labeling, a North American trial that enrolled 544 postmenopausal women and an international trial that enrolled 619 postmenopausal women who had undergone hysterectomy. As in the other study, all women received calcium supplementation at 400 to 600 mg/day and met similar entry criteria. Raloxifene was administered at a dose of 60 mg once daily. The calcium supplemented placebo-treated patients lost about 1% of bone mineral density over 24 months. Raloxifene increased bone mineral density by 1.3% to 2% compared with placebo (see Figure 2).

Figure 2: Effects of Raloxifene 60 mg Plus Calcium Supplementation on Bone Mineral Density After 24 Months of Therapy



The effects of raloxifene on lipid metabolism were also evaluated in a 6-month study, summarized in the product labeling, enrolling 390 postmenopausal women. Patients received either raloxifene 60 mg/day, oral continuous combined estrogen/progestin (conjugated estrogens 0.625 mg plus medroxyprogesterone 2.5 mg) or placebo. As in the other study, raloxifene reduced serum total cholesterol and LDL cholesterol, with no effects on HDL cholesterol or triglycerides. Results are summarized in Table 2.

Table 2: Serum Lipid Concentrations (mean percent change from baseline)

Serum Lipid	Placebo	Raloxifene	HRT
Cholesterol			
Total	0.9%	-6.6%*	-4.4%*
LDL	1%	-10.9%*	-12.7%*
HDL	0.9%	0.7%**	10.6%*
Triglycerides	-0.3%	-4.1%**	20%*

\* Value is significantly different from that for placebo (p<0.05).

\*\* Value is significantly different from that for estrogen/progestin (p<0.05).

HRT = hormone replacement therapy

Studies evaluating the ability of raloxifene to prevent fractures in postmenopausal women with established osteoporosis are ongoing.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Raloxifene is contraindicated in women who are or may become pregnant, women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis, and women known to be hypersensitive to raloxifene or other product ingredients. It also should not be used in premenopausal women, women receiving systemic estrogens, women who are lactating or in pediatric patients.

An increased risk of venous thromboembolic events similar to the risk with ERT was observed during raloxifene treatment. The greatest risk occurs during the first 4 months of therapy. Raloxifene should be discontinued at least 72 hours prior to and during prolonged immobilization and should be resumed only after the patient is fully ambulatory. Patients should avoid prolonged restrictions of movement during travel. Risk may be increased in women at risk of thromboembolic disease for other reasons, such as congestive heart failure or active malignancy. In contrast, patients on estrogen replacement therapy have not had an increased risk of thrombophlebitis or thromboembolic disease.

The concurrent use of raloxifene with systemic estrogen or hormone replacement therapy has not been studied and therefore is not recommended at this time.

Raloxifene is categorized in Pregnancy Category X. It caused retardation of fetal development and developmental abnormalities in animal studies. It also should not be administered to lactating women or pediatric patients.

Safety and efficacy have not been evaluated in men.

**ADVERSE REACTIONS:** Common side effects considered raloxifene-related include leg cramps and hot flashes. Raloxifene is not effective in reducing hot flashes or flushes associated with estrogen deficiency, and in some asymptomatic patients, hot flashes may occur upon initiation of raloxifene therapy. Other side effects reported commonly in clinical trials have included nausea, dyspepsia, vomiting, weight gain, edema, arthralgia, myalgia, depression, sinusitis, rash, sweating, vaginitis and leukorrhea. Consult the package literature for a complete list of adverse effects reported during raloxifene clinical trials. Table 5 summarizes adverse effects reported in clinical trials comparing raloxifene with estrogen-progestin replacement therapy.

Table 5: Adverse Effects Reported in Comparative Studies of Raloxifene and HRT

Adverse Effect	Raloxifene	HRT Continuous Combined	HRT Cyclic
<b>Urogenital</b>			
Breast pain	4.4%	37.5%	29.7%
Vaginal bleeding	6.2%	64.2%	88.5%
<b>Digestive</b>			
Flatulence	1.6%	12.5%	6.4%
<b>Cardiovascular</b>			
Hot flashes	28.7%	3.1%	5.9%
<b>Body as a whole</b>			
Infection	11%	0	6.8%
Abdominal pain	6.6%	10.4%	18.7%
Chest pain	2.8%	0	0.5%

HRT continuous combined (conjugated estrogens 0.625 mg plus medroxyprogesterone 2.5 mg)

HRT cyclic (conjugated estrogens 0.625 mg for 28 days, with concomitant medroxyprogesterone acetate or norethindrone 1 mg for 12 days)

Raloxifene has not been associated with breast enlargement, breast pain or an increased risk of breast cancer. It has not been adequately studied in patients with a history of breast cancer.

Raloxifene has not been associated with endometrial proliferation. Patients experiencing unexplained uterine bleeding while on raloxifene should be closely evaluated.

**DRUG INTERACTIONS:** Cholestyramine reduces raloxifene absorption and enterohepatic cycling and therefore should not be coadministered with raloxifene.

In single-dose studies, a 10% reduction in prothrombin time was observed when raloxifene and warfarin were coadministered. Data on chronic concomitant administration are not yet available. Prothrombin time should be monitored if raloxifene is administered concurrently with warfarin.

Raloxifene did not affect the binding of warfarin, phenytoin or tamoxifen. Until more data are available, however, raloxifene should be administered with caution with other highly protein bound medications such as clofibrate, indomethacin, naproxen, ibuprofen, diazepam and diazoxide.

Ampicillin reduced raloxifene absorption and peak concentrations, consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, overall systemic exposure was not reduced.

**DOSING:** The recommended dose of raloxifene is 60 mg once daily administered any time of day without regard to meals. Raloxifene should be taken with supplemental calcium and vitamin D if dietary intake is inadequate.

**COST:** \$1.98/60 mg tab AWP

**CONCLUSION:** Raloxifene reduces bone resorption and bone loss in postmenopausal women, although to an apparently lesser extent than estrogen replacement therapy or alendronate. Raloxifene can also decrease total cholesterol and LDL-cholesterol levels, but has no effect on HDL cholesterol or triglyceride levels. Raloxifene's effectiveness in preventing fractures or cardiovascular disease has yet to be demonstrated. The risks associated with the use of raloxifene include hot flashes and thromboembolic events. Raloxifene should be considered an alternative to the other forms of therapy for the prevention of osteoporosis, particularly in women unable to or unwilling to use hormone replacement or alendronate therapy.

## PROGESTERONE, USP - PROMETRIUM™ (Solvay Pharmaceuticals) 3S

**INDICATIONS:** Oral micronized progesterone is indicated for the treatment of secondary amenorrhea due to progesterone deficiency. An additional application is currently under review for hormone replacement therapy. The FDA-approved indications for oral micronized progesterone and the oral progestins are summarized in Table 1.

Table 1: FDA-Approved Indications:

Indication	Medroxyprogesterone Acetate	Norethindrone Acetate	Progesterone USP
Abnormal uterine bleeding due to hormonal imbalance	X	X	
Endometriosis		X	
Secondary amenorrhea	X	X	X

**CLINICAL PHARMACOLOGY:** Progesterone is a hormone produced by the ovaries, placenta and adrenal glands. *Prometrium* contains progesterone that is synthesized from yams and is chemically identical to the progesterone produced by the ovaries. It is micronized to improve the oral bioavailability of the product.

Information published on micronized progesterone involves several different products. *Prometrium* capsules contain micronized progesterone 100 mg in peanut oil. In Europe, the formulation (Utrogestan, Besins-Iscovesco, Paris, France) contains micronized progesterone 100 mg in arachidonic oil.

**PHARMACOKINETICS:** Peak serum concentrations are reached within 3 hours following oral administration. The absolute oral bioavailability is not known. Intersubject variability in absorption following oral administration has been quite variable and product dependent. Administration of progesterone as micronized progesterone in oil results in a higher peak, greater AUC and more rapid absorption than administration of progesterone as powdered plain milled progesterone in a capsule, powdered micronized progesterone in a capsule, plain milled progesterone in oil, or micronized progesterone in enteric-coated capsules. Bioavailability of a micronized progesterone tablet was comparable to a progesterone vaginal pessary, although in another study, micronized progesterone showed better bioavailability with vaginal administration than oral. Oral capsules (200 mg by Utrogestan) produced a lower peak level, shorter time to peak and reduced bioavailability compared to intramuscular progesterone 50 mg. The relative bioavailability of this micronized progesterone product was 8.6% compared to the intramuscular product.

Administration with food can result in an increased bioavailability. When administered with a high-fat meal or 2 hours after a high-fat meal, the peak progesterone level was increased 9% compared to administration in the fasted state. However, administration 4 hours after the high-fat breakfast resulted in a 193% increase in peak levels. The AUC increased 47%, 50% and 102% following administration with breakfast, 2 hours after breakfast and 4 hours after breakfast, respectively.<sup>1</sup> Administration with high-fiber meals also increased the drugs bioavailability.

The pharmacokinetic parameters of micronized progesterone in soft gelatin capsules (*Prometrium*) are summarized in Table 2.

Table 2: Pharmacokinetics of Oral Micronized Progesterone:

Parameter	Daily Dose		
	100 mg	200 mg	300 mg
C <sub>max</sub> (ng/mL)	17.3	38.1	60.6
T <sub>max</sub> (hr)	1.5	2.3	1.7
AUC (0-10) (ng hr/mL)	43.3	101.2	175.7

Twice-daily administration of micronized progesterone is recommended to maintain physiologic progesterone levels when used in hormone replacement therapy; however, most studies have evaluated once-daily administration.

Serum protein binding is 96% to 99% and primarily involves serum albumin and transcortin. Progesterone is metabolized primarily by the liver to pregnanediols and pregnanolones, which are conjugated in the liver to glucuronide and sulfate metabolites. The glucuronide and sulfate conjugates are excreted in the bile and urine. Metabolites that are excreted in the bile may be deconjugated and metabolized in the gut via reduction, dehydroxylation and epimerization.

Pharmacokinetics have not been studied in patients with hepatic or renal dysfunction. However, because progesterone is extensively hepatically metabolized, use in patients with severe liver dysfunction or disease is contraindicated. Patients with mild-to-moderate hepatic dysfunction should be monitored closely. Progesterone should be used with caution and closely monitored in patients with renal dysfunction, because some of the metabolites are excreted renally.

## **EFFICACY:**

### *Secondary Amenorrhea*

In a double-blind, placebo controlled study evaluating micronized progesterone (*Prometrium*) 300 mg/day for 10 days in 41 women with secondary amenorrhea of at least 90 days duration, withdrawal bleeding occurred in 80% of women treated with micronized progesterone compared to 10% of women in the placebo group. In another double-blind, placebo controlled study enrolling 45 women, micronized progesterone (*Prometrium*) 400 mg/day for 10 days induced complete secretory changes in the endometrium in 45% of progesterone-treated women compared to none of the placebo-treated women.

Micronized progesterone (Utrogestan) was also evaluated in the treatment of secondary amenorrhea in a double-blind study enrolling 60 women. Patients were treated with a 10-day course of oral micronized progesterone 300 mg, oral micronized progesterone 200 mg or placebo. Ninety percent of women treated with 300 mg, 58% of women treated with 200 mg and 29% of the placebo group ( $p < 0.0002$  for 300 mg versus placebo) had withdrawal bleeding.

Micronized progesterone (Utrogestan) was compared with norethisterone in 80 women with dysfunctional uterine bleeding in another study. Patients presented with metrorrhagia, hypermenorrhea, menorrhagia, irregular menstruation or a myomatous uterus. Endometrial histology revealed cystic glandular hyperplasia, proliferative endometrium or incomplete maturation of the endometrium, all indicating a need for progesterone therapy. Patients were treated with either norethisterone 5 mg three times daily or micronized progesterone 100 mg three times daily. Both therapies were continued for 10 days, from day 15 to day-24 of the menstrual cycle. Both agents transformed the endometrium to a normal secretory endometrium in the majority of patients during therapy, but results were generally not maintained following discontinuation of therapy. Although efficacy appeared comparable, norethisterone produced more deleterious effects on lipid and hormonal profile but micronized progesterone was associated with a greater drop out rate.

### *Postmenopausal Hormone Replacement Therapy*

Oral micronized progesterone was evaluated in a hormone replacement therapy regimen in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a 3-year double-blind, placebo controlled trial enrolling 875 postmenopausal women. Participants received, in 28-day cycles, placebo, conjugated estrogens 0.625 mg (CEE), conjugated estrogens 0.625 mg plus medroxyprogesterone acetate 10 mg/d for the first 12 days (CEE + MPA [cyc]), conjugated estrogens 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d (CEE + MPA [cont]) or conjugated estrogens 0.625 mg/d plus micronized progesterone (*Prometrium*) 200 mg/d for the first 12 days (CEE + MP [cyc]). Endometrial hyperplasia occurred more frequently in women treated with estrogen alone. Each of the progestin regimens protected against hyperplasia to a similar extent. Bone mineral density increased to a similar extent in each of the

estrogen- and estrogen-plus-progestin-treatment groups. The effects on lipoprotein levels are summarized in Table 3. Estrogen alone produced the most favorable lipoprotein changes but each of the combination regimens was better than placebo. Micronized progesterone preserved more of the favorable effects of estrogen on HDL cholesterol. Women assigned to estrogen therapy gained less weight during the 3-year study than those treated with placebo. Similar effects on weight and girth were observed for each of the active-treatment regimens.

Table 3: Effects on Lipoproteins (mg/dL) after 36 Months of Therapy:

Lipoproteins	Placebo	CEE only	CEE + MPA (cyc)	CEE + MPA (cont)	CEE + MP (cyc)
HDL-C	-1.2	5.6	1.6	1.2	4.1
LDL-C	-4.1	-14.5	-17.7	-16.5	-14.8
Total Cholesterol	-4.2	-7.6	-14.1	-14	-7.8
Triglycerides	-3.2	13.7	12.7	11.4	13.4

#### Luteal Phase Defects

The efficacy of oral micronized progesterone in correcting luteal phase defects in women who had previously responded with vaginal progesterone suppositories was evaluated in an open study enrolling seven women. Patients were treated with oral capsules containing micronized progesterone 200 mg in a safflower oil base three times daily. Therapy was initiated 3 days after an increase in basal body temperature. Endometrial biopsies were obtained following a negative pregnancy test 10 to 12 days after ovulation. All patients had their luteal phase defect corrected by oral micronized progesterone as assessed by endometrial biopsy. Five of the 7 patients preferred or greatly preferred the oral micronized progesterone to vaginal progesterone. None of the patients preferred vaginal progesterone to oral. Sedation was the most common side effect.

Oral micronized progesterone (Utrogestan, Laboratories Besins Iscoresco, Paris, France) was compared with vaginal progesterone (*Crinone* 8% gel) for luteal support of patients undergoing an *in vitro* fertilization procedure in an open-label, randomized study enrolling 283 patients. Patients received either vaginal progesterone 90 mg daily or oral micronized progesterone 100 mg each morning and 200 mg each evening starting 24 hours after embryo transfer and continuing until day-30 in cases of implantation. Pregnancy rates did not differ between treatment groups. No differences in rates of spontaneous abortion or delivery or in the ratio of newborn babies per embryo transferred were observed. Safety profiles were also comparable, although patients treated with oral progesterone experienced more drowsiness, irritability and decreased libido. In another study, oral micronized progesterone 300 mg/day at bedtime provided better luteal phase support than micronized progesterone 300 mg/day administered vaginally. In comparison with human chorionic gonadotropin, oral micronized progesterone (Utrogestan) 400 mg/d was less effective in providing luteal phase support in patients undergoing *in vitro* fertilization as manifested by lower implantation rate and pregnancy rates. In another study, oral micronized progesterone (compounded, safflower oil in capsules) 200 mg four times daily with meals starting immediately after oocyte retrieval was evaluated in comparison to placebo in 70 women undergoing *in vitro* fertilization. Progesterone therapy produced higher progesterone levels and a longer duration of the luteal phase than placebo.

#### Preterm Labor

Oral micronized progesterone (Utrogestan) was also evaluated in the treatment of menace of preterm labor. In 44 patients presenting with a change in the uterine cervix or regular uterine contractions at least every 10 minutes and persisting after 1 hour of rest, ritodrine intravenous was administered plus oral micronized progesterone in 22 patients and placebo in 22 patients. Progesterone was dosed at 400 mg every 6 hours during the first 24 hours, then 400 mg every 8 hours during the following 24 hours and 300 mg every 8 hours from day-3 on. Pregnancy was prolonged by 6.4 weeks in the placebo group and by 6

weeks in the progesterone group. Eight patients in the placebo group and six in the progesterone group had preterm delivery. Patients receiving progesterone required significantly less ritodrine and shorter duration of hospitalization.<sup>31</sup>

#### *Other*

Premenstrual syndrome symptoms can be improved with the administration of oral micronized progesterone (Utrogestan) 100 mg every morning and 200 mg at bedtime for 10 days prior to the anticipated menstrual period. No benefit was observed with oral micronized progesterone 300 mg four times daily in the treatment of severe premenstrual syndrome.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Oral micronized progesterone (*Prometrium*) is contraindicated in patients with known sensitivity to *Prometrium*, peanuts or any of its ingredients (peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow #10 and FD&C red #40). Micronized progesterone is also contraindicated in patients with known or suspected pregnancy; thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a history of these conditions; severe liver dysfunction or disease; known or suspected malignancy of breast or genital organs; undiagnosed vaginal bleeding or missed abortion or as a diagnostic test for pregnancy.<sup>1</sup> The contraindications, warnings and precautions included in the labeling for *Prometrium* are similar to those in the labeling for medroxyprogesterone acetate and norethindrone acetate. As with the other progestins, therapy should be discontinued in patients who developed sudden partial or complete vision loss or sudden onset of proptosis, diplopia or migraine.

Progesterone is categorized in Pregnancy Category X. Use in pregnancy is not recommended by the manufacturer. A case of cleft palate was observed in the child of a woman who received oral micronized progesterone (*Prometrium*) during early pregnancy. Rare instances of fetal death have been reported in pregnant women prescribed micronized progesterone (*Prometrium*) for unapproved indications, although causality has not been established.<sup>1</sup> Most sources do not regard progesterone as a teratogen or source of fetal toxicity and numerous studies have evaluated oral micronized progesterone use in early pregnancy, particularly in conjunction with *in vitro* fertilization programs.

Micronized progesterone should be administered to nursing mothers only when clearly necessary. Progestins have been identified in the milk of nursing mothers receiving progestins.

**ADVERSE REACTIONS:** The most common adverse effects reported during therapy with oral micronized progesterone have included fatigue, headache, dizziness, abdominal pain or distention, diarrhea, nausea, coughing, breast pain, musculoskeletal pain, emotional lability, irritability and viral infection.<sup>1</sup>

Dizziness, drowsiness, fatigue, confusion and impaired recall have been reported with oral progesterone administration. These effects appear to be associated with progesterone metabolites and occur more frequently with high doses.<sup>11,34-36</sup> Bedtime administration can lessen the effects from drowsiness.<sup>11</sup>

**DRUG INTERACTIONS:** The metabolism of progesterone is inhibited by ketoconazole. The clinical significance of progesterone metabolism inhibition by ketoconazole or other inhibitors of CYP 3A4 is not known.

**DOSING:** The recommended dose in the treatment of secondary amenorrhea is 400 mg daily as a single dose in the evening for 10 days.

**PRODUCT AVAILABILITY:** Oral micronized progesterone received FDA approval in May 1998. It is available as soft gelatin capsules containing 100 mg micronized progesterone in peanut oil.

**CONCLUSION:** Prescribers who wish to use progesterone alone or in combination with an estrogen have had to rely on compounded tablets, capsules or various vaginal products. However, some of these formulations were associated with poor bioavailability. After the marketing of *Crinone* and now *Prometrium* there is no reason for most patients to use the compound products. Instead, the commercial product should be used when possible.

RIZATRIPTAN Tablets - Maxalt® and Orally Disintegrating Tablets - Maxalt-MLT™ by Merck Sharp & Dohme - 1S

**INDICATIONS:** Rizatriptan is indicated for the acute treatment of migraine with or without aura in adults. It is not intended for prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraines. Safety and efficacy have not been established in cluster headache at this time. Rizatriptan has the same indications as naratriptan, sumatriptan and zolmitriptan.

**CLINICAL PHARMACOLOGY:** Rizatriptan is a 5-hydroxytryptamine<sub>1B/1D</sub> receptor agonist. Rizatriptan has weak affinity for 5-HT<sub>1A</sub>, 5-HT<sub>1E</sub> and 5-HT<sub>1F</sub> receptor subtypes and the 5-HT<sub>7</sub> receptor, but no activity at the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor subtypes or at alpha- or beta-adrenergic, dopaminergic, muscarinic or benzodiazepine receptors.

Migraine headaches are associated with activation of the trigeminovascular system, which results in vasodilatation and neurogenic inflammation. Rizatriptan acts like naratriptan, sumatriptan and zolmitriptan on the trigeminovascular system to modulate cranial nociceptive input, thereby constricting cranial blood vessels and inhibiting the release of sensory neuropeptides during trigeminal activation. Rizatriptan is not extensively distributed into the central nervous system, but *ex vivo* it has been more cranioselective and more effective than sumatriptan in causing contraction of middle meningeal arteries.

**PHARMACOKINETICS:** Rizatriptan is extensively absorbed after oral administration, but it has a mean oral absolute bioavailability of 45% with the tablet formulation due to extensive first-pass metabolism. Mean peak plasma concentrations are reached in about 1 to 1.5 hours after administration of the traditional tablets and about 1.6 to 2.5 hours after administration of the orally disintegrating tablets. The presence of a migraine does not affect rizatriptan pharmacokinetics. Administration with food delays the time to reach the peak concentration by about 1 hour and increases the AUC (20%), but does not alter the peak concentration or the half-life. In studies, rizatriptan was administered without regard to meals.

The plasma half-life averages 2 to 3 hours. Rizatriptan undergoes metabolism via oxidative deamination by monoamine oxidase-A to form an inactive indole acetic acid metabolite. N-monodesmethyl-rizatriptan, a minor metabolite present in concentrations approximately 14% of those of rizatriptan, has activity similar to rizatriptan. Other minor metabolites are inactive. Rizatriptan and its metabolites are primarily excreted renally. Approximately 14% of the administered dose is excreted unchanged in the urine.

Pharmacokinetics are comparable in the elderly and younger subjects. Plasma concentrations are increased in females compared to males. Plasma concentrations are not increased in patients with mild hepatic insufficiency, but are increased approximately 30% in patients with moderate hepatic dysfunction. In patients with renal impairment (CrCl 10 to 60 mL/min/1.73 m<sup>2</sup>), the AUC of rizatriptan was not altered compared to healthy subjects. The AUC was increased approximately 44% in patients on hemodialysis.

Table 1: Summary of Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan Pharmacokinetics:

Parameter	Naratriptan	Rizatriptan		Zolmitriptan		Sumatriptan	
	Oral	Tablets	Disintegrating Tablets	Oral (5 mg)	Oral (10 mg)	Oral (100 mg)	Nasal (20 mg)
C <sub>max</sub> (mcg/L)	--	--	--	7.3-9.1	13.4-25.2	51-54	14.4
T <sub>max</sub> (h)	2-4	1-1.5	1.6-2.5	1.5	2-3.5	1.5-2.5	1
AUC <sub>0-12</sub> (mcg/Lh)	--	--	--	--	--	197	--
AUC <sub>0-infinity</sub> (mcg/Lh)	--	--	--	51.9-62.1	87.4-173.8	--	53.5
Bioavailability (%)	70	45	--	40-46	46-49	14	15
V <sub>d</sub> (L)	170	110-140	110-140	--	402	--	--
CL (L/h)	--	--	--	--	123.6	--	--
CL <sub>r</sub> (L/h)	13.2	--	--	--	10-22.3	11.9	--
t <sub>1/2</sub> (h)	6	2-3	2-3	2.8-3.4	2.5-3.7	2-2.5	2
t <sub>1/2</sub> (h) renal dysfunction	6-11	--	--	--	--	--	--
fe	50%	14%	14%	8%	8%	22%	--

C<sub>max</sub> = maximum plasma concentration, T<sub>max</sub> = time to C<sub>max</sub>, AUC<sub>0-12</sub> = area under the curve from 0 to 12 hours, AUC<sub>0-infinity</sub> = AUC from 0 hours to infinity, V<sub>d</sub> = volume of distribution, CL = total plasma clearance, CL<sub>r</sub> = renal plasma clearance, t<sub>1/2</sub> = plasma elimination half-life; fe = fraction excreted unchanged in the urine

**COMPARATIVE EFFICACY:** Four placebo controlled trials evaluating rizatriptan tablets are summarized in the package literature. Additional results from these studies were also published or presented in abstracts. Patients in these studies were instructed to treat a moderate-to-severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours in one study or up to 4 hours in the other three studies. A second rizatriptan dose was allowed 2 to 24 hours after the first in two of the studies. Rescue analgesics and antiemetics were allowed 2 hours after the initial rizatriptan dose in all four studies. Two-hour response rates are summarized in Table 2.

Table 2: Two-hour Rizatriptan Response Rates:

Study *	Placebo	Rizatriptan 5 mg	Rizatriptan 10 mg
1 (n=1218)	35%	62% **	71% ***,***
2 (n=402)	37%	--	77% **
3 (n=432)	23%	63% **	--
4 (n=708)	40%	60% **	67% **
MLT (n=312)	47%	66% **	66% **

\* Studies 1-4 evaluated the standard tablet formulation, study MLT evaluated the orally disintegrating tablets  
 \*\* p value <0.05 in comparison with placebo  
 \*\*\* p value < 0.05 in comparison with rizatriptan 5 mg

Results of another study assessing the efficacy of the rizatriptan orally disintegrating tablets are also summarized in the package literature. Patients were assigned placebo or 5 mg or 10 mg rizatriptan and instructed to treat a moderate-to-severe headache. Two-hour response rates are summarized in Table 2.

Rizatriptan 10, 20 and 40 mg doses were also compared with oral sumatriptan 100 mg and placebo in the treatment of acute migraine in a double-blind study enrolling 449 patients. Patients were instructed to treat a moderate-to-severe migraine attack with the assigned study medication. After 2 hours, if the moderate-to-severe headache persisted, patients could take an optional second dose of an alternate medication. Patients initially treated with placebo received rizatriptan 40 mg; patients initially treated with 10, 20 or 40 mg rizatriptan received 30 mg or 20 mg rizatriptan or placebo; and patients initially treated with sumatriptan received placebo. Rescue analgesics were permitted after 4 hours. Headache relief, defined as improvement in headache pain from moderate or severe to mild or no headache at 2 hours after drug administration was assessed. Results are summarized in Table 3. Rizatriptan 10 mg and 20 mg were comparable to sumatriptan 100 mg. Only at the 40 mg dose was rizatriptan superior to sumatriptan, and at this dose it was associated with frequent adverse effects. At all doses rizatriptan and sumatriptan were more effective than placebo in relieving nausea, photophobia and phonophobia at 2 hours after the initial treatment (p<0.01).

Table 3: Rizatriptan and Sumatriptan Study Results:

	Placebo	Sumatriptan 100 mg	Rizatriptan 10 mg	Rizatriptan 20 mg	Rizatriptan 40 mg
Headache relief at 1 hour	14%	24%	25%	29% <sup>a</sup>	39% <sup>b</sup>
Headache relief at 2 hours	18%	46% <sup>c</sup>	52% <sup>c</sup>	56% <sup>c</sup>	67% <sup>c,d</sup>
Pain free at 2 hours	3%	22% <sup>e</sup>	26% <sup>e</sup>	35% <sup>e</sup>	49% <sup>e</sup>
Functioning normally at 2 hours	5%	25% <sup>e</sup>	27% <sup>e</sup>	32% <sup>e</sup>	29% <sup>e</sup>
Use of second dose at 2 hours	83% <sup>f</sup>	54%	46%	44%	33% <sup>g</sup>
Headache recurrence within 24 hours	36%	41%	41%	53%	42%
Median time to headache recurrence (h)	5	19	14	14	16
Patients with adverse effects	36%	46%	48%	67%	83%

a. p value = 0.02 compared to placebo  
 b. p value < 0.01 compared to placebo  
 c. p value < 0.001 compared to placebo  
 d. p value = 0.011 compared to sumatriptan  
 e. p value < 0.005 compared to placebo  
 f. p value < 0.001 compared to rizatriptan and sumatriptan  
 g. p value = 0.003 compared to sumatriptan

A dose-finding, placebo controlled study enrolling 417 patients also evaluated the efficacy of rizatriptan in the treatment of moderate-to-severe migraine attack. Patients treated a moderate-to-severe migraine with rizatriptan 2.5 mg, 5 mg or 10 mg, or placebo, and assessed headache severity, functional disability and migraine symptoms at 0.5, 1, 1.5, 2, 3 and 4 hours post-dose. A second dose was allowed after 2 hours, although rizatriptan-treated patients received a placebo second dose and placebo-treated patients received rizatriptan for the second dose. Results are summarized in Table 4. The 5 mg and 10 mg doses were comparable in efficacy, and both were more effective than placebo. Quality of life was also improved in the group receiving the 10 mg dose.

Table 4: Rizatriptan Study Results:

	Placebo	Rizatriptan 2.5 mg	Rizatriptan 5 mg	Rizatriptan 10 mg
Headache relief at 1 hour	20.9%	20%	31.5%	30.3%
Headache relief at 2 hours	17.9%	21.3%	45.4%*	47.6%*
Pain free at 2 hours	3%	9.3%	22.3%*	27.6%*
Functioning normally at 2 hrs	9%	13%	28%	32%
Use of second dose at 2 hrs	85%	72%	55%**	52%**
Headache recurrence within 24 hours	33.3%	40%	42.1%	36.5%

\* p value <0.01 compared to placebo

\*\* p value <0.001 compared to placebo

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** The contraindications, warnings and precautions associated with rizatriptan are nearly identical to those of naratriptan, sumatriptan and zolmitriptan.

As with naratriptan, sumatriptan and zolmitriptan, rizatriptan should not be administered to patients with documented ischemic or vasospastic coronary artery disease. In addition, its use should be avoided in patients with a number of risk factors for coronary artery disease unless a cardiovascular evaluation indicates the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disorders. In patients with risk factors predictive of coronary artery disease but with a satisfactory cardiovascular evaluation, the first dose of rizatriptan should be administered in a physician's office or other similarly staffed and equipped medical facility. An electrocardiogram may be considered during the interval immediately following the first dose. Periodic cardiovascular evaluation should be considered for intermittent users of rizatriptan with risk factors or who acquire risk factors predictive of coronary artery disease.

Although rizatriptan appears to produce less coronary vasoconstriction than sumatriptan in *ex vivo* studies, a few of the clinical trials have indicated rizatriptan causes less chest pain than sumatriptan. As outlined in the package insert, it should not be used in populations at risk of these side effects.

Pregnancy Category C.

Safety and effectiveness of rizatriptan, sumatriptan and zolmitriptan in pediatric patients have not been established. Naratriptan at doses of 0.25 to 2.5 mg has been evaluated in a small number of pediatric migraine patients aged 12 to 16 years in a placebo controlled study. Efficacy was similar between the groups, and the adverse effects were similar in nature to those reported in adults.

**ADVERSE REACTIONS:** The adverse effects reported with rizatriptan in clinical trials have been quite similar to those reported with naratriptan, sumatriptan and zolmitriptan. The most common adverse effects have included asthenia/fatigue, somnolence, pain/pressure sensation and dizziness.

Table 6: Adverse Effects Reported in Naratriptan Clinical Trials

Adverse Effect	Placebo (n=627)	Rizatriptan	
		5 mg (n=977)	10 mg (n=1167)
Atypical sensations	4%	4%	5%
Paresthesia	<2%	3%	4%
Pain and pressure sensations	3%	6%	9%
Chest pain: tightness/pressure and/or heaviness	1%	<2%	3%
Neck/throat/jaw: pain/tightness/pressure	1%	<2%	2%
Regional pain: tightness/pressure/heaviness	0	<1%	2%
Pain, location unspecified	<2%	3%	3%
Gastrointestinal	8%	9%	13%
Dry mouth	1%	3%	3%
Nausea	4%	4%	6%
Neurological	11%	14%	20%
Dizziness	5%	4%	9%
Headache	<1%	<2%	2%
Somnolence	4%	4%	8%
Other			
Asthenia/fatigue	2%	4%	7%

**DRUG INTERACTIONS:** Because rizatriptan is metabolized via monoamine oxidase A (MAO-A), plasma concentrations of rizatriptan may be increased by drugs that inhibit MAO-A, including selective MAO-A inhibitors (eg, moclobamide) and nonselective MAO inhibitors (eg, isocarboxazid, phenelzine, tranylcypromine and pargyline). Rizatriptan should not be administered with these agents.

As with naratriptan, sumatriptan and zolmitriptan, rizatriptan should not be administered concurrently with MAO inhibitors, ergotamine or ergot-type medications. To avoid additive vasospastic effects, concomitant use of other 5HT<sub>1B/1D</sub> agonists within 24 hours of rizatriptan is not recommended. In addition, caution is advised when any of these agents is administered concurrently with other serotonergic medications. Selective serotonin reuptake inhibitors may cause weakness, hyperreflexia and incoordination when administered with 5HT<sub>1</sub> agonists. Patients should be closely monitored if rizatriptan is administered concomitantly with an SSRI. Drugs known to interact with naratriptan, rizatriptan, sumatriptan and/or zolmitriptan are summarized in Table 7.

Propranolol increased the rizatriptan AUC by 70%. Patients taking propranolol should be treated with the 5 mg dose of rizatriptan. No drug interaction has been reported between rizatriptan and nadolol or metoprolol. Zolmitriptan levels are also increased by propranolol.

Table 7: Drug Interactions Reported with Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan:

Drugs	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Cimetidine				X
Ergotamine or ergot-type medications	X	X	X	X
MAO-A inhibitors	X	X	X	X
Oral contraceptives	X			X
Propranolol		X		X
Selective serotonin reuptake inhibitors (SSRIs)	X	X	X	X

**DOSING:** Single doses of 5 and 10 mg are effective in the therapy of acute migraine. The 10 mg dose may provide greater effect than the 5 mg dose. Doses should be separated by at least 2 hours, and no more than 30 mg should be taken in any 24-hour period. Patients taking propranolol should receive the 5 mg dose, and no more than three doses (15 mg) should be used in any 24-hour period. The orally disintegrating tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva. Administration with liquid is not necessary. Dosage recommendations for naratriptan, rizatriptan, sumatriptan and zolmitriptan are summarized in Table 8.

Table 8: Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan Dosage Recommendations:

Agent	Approved Dose	Repeat Dose	Maximum Dose in 24 Hours
Naratriptan	1-2.5 mg	Dose may be repeated after 4 hours	5 mg
Rizatriptan	5-10 mg	Dose may be repeated after 2 hours	30 mg
Sumatriptan	25 - 100 mg	Up to 100 mg after 2 hours	300 mg
Zolmitriptan	1-5 mg	Dose may be repeated after 2 hours	10 mg

**PRODUCT AVAILABILITY:** Rizatriptan received FDA approval in June 1998. It is available as 5 mg and 10 mg tablets and peppermint flavored orally disintegrating tablets. Available naratriptan, rizatriptan, sumatriptan and zolmitriptan dosage forms are listed in Table 9. The orally disintegrating tablets are packaged in a blister pack within an outer aluminum pouch. The blister pack containing the oral disintegrating tablets should not be removed from the outer pouch until just prior to dosing. At that time the blister pack should be peeled open with dry hands and the tablet placed on the tongue. The tablet should not be pushed through the blister.

Table 9: Dosage Forms Available:

Agent	Dosage Forms	Cost (AWP)
Naratriptan	1 mg tablets 2.5 mg tablets	\$14.96/2.5 mg tab
Rizatriptan	5 mg tablets 10 mg tablets 5 mg orally disintegrating tablets* 10 mg orally disintegrating tablets*	\$14.07/tab  <i>All priced equally.</i>
Sumatriptan	25 mg tablets 50 mg tablets 6 mg injection 5 mg nasal spray 20 mg nasal spray	\$11.88/tab \$11.88/tab \$43.96/6 mg inj. \$12.22/spray \$12.22/spray
Zolmitriptan	2.5 mg tablets 5 mg tablets	\$13.13/2.5 mg tab \$14.92/5 mg tab

\* = Contains aspartame

**CONCLUSION:** Rizatriptan is a serotonin agonist effective in the therapy of migraine headache. It is available as a traditional tablet and a unique oral rapidly disintegrating tablet that is taken without a liquid. Peak concentrations are reached more slowly with the orally disintegrating tablet so it may not produce as rapid a response as the traditional tablet, however, it may be more convenient. It may also be better tolerated in patients with nausea since it is peppermint flavored and does not need to be taken with liquid and is an alternative to injectable or rectal therapies. It has oral bioavailability, time to peak concentrations and half-life comparable to zolmitriptan. Studies directly comparing rizatriptan with naratriptan or zolmitriptan are not available. Rizatriptan 10 mg has been as effective as sumatriptan 100 mg and may produce a more rapid response. Rizatriptan will offer an alternative to naratriptan, sumatriptan and zolmitriptan therapy for patients in whom therapy with a serotonin agonist is desired. Some patients may respond better to one agent than the other, therefore, patients failing to fully respond to one agent will likely be tried on another or dihydroergotamine, unless contraindicated.

## ORLISTAT - Xenical® by Roche

A lipase inhibitor, selectively inhibits fat absorption up to 25-30%.

In a one year trial, 57% of patients lost  $\geq 5\%$  of body weight vs. 31% on placebo. Patient's LDL reduced by 8-10%, blood pressure reduced 1.5 - 2 mm Hg systolic and diastolic, Hb A1c reduced  $\sim 0.2\%$  and mean weight loss was  $\sim 3-4$  kgs more than placebo.

### Dose

120 mg TID ( $< 1\%$  bioavailable) - take with multi-vitamin but 3 hours later after Xenical® dose (decrease vitamin D, E, and beta carotene)

### Significant GI Side Effects

	1st Year	2nd Year
Oily spotting	26.6%	4.4%
Flatus with discharge	23.9%	2.1%
Fecal urgency	22.1%	2.8%
Increased defecation	10.8%	2.6%
Fecal incontinence	7.7%	1.8%

(discontinuation rate secondary to GI effects 1.7%)

During clinical trials, nine patients on active drug developed breast cancer vs. an expected 3.25 cases, 5/9 cases were diagnosed within six months, too soon to be drug related? Typically believed to take 5-8 years to develop.

## SILDENAFIL - Viagra® by Pfizer - "1-P"

**MECHANISM:** A selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE 5). Penile erection involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO activates guanylate cyclase which increases cGMP and produces smooth muscle relaxation promoting inflow of blood and an erection. Sildenafil inhibits PDE-5 which normally degrades cGMP in the corpus cavernosum resulting in an increase in cGMP.

Sildenafil is very selective for PDE-5

~ 80 fold less active vs. PDE-1

> 1,000 fold less active vs. PDE-2, 3 and 4 (~ 4000 times less active vs. PDE-3 which is involved in cardiac contractility) but only ~ 10 fold less active vs. PDE-6 (retina/color vision)

**PHARMACOKINETICS:** Sildenafil is metabolized by CYP 3A4 to an active metabolite (~ 50% as active vs. parent). Oral bioavailability is ~ 40%, peak concentration ~ 1 hour fasting vs. ~ 2 hours with food.  $T_{1/2\beta}$  ~ 4 hours for both the parent compound and the active metabolite.

- Patients  $\geq$  65 y/o have reduced clearance and ~ 40% increase in free plasma concentration.
- Patients with renal impairment ( $Cl_{cr} < 30$  cc/min) have peak concentrations and AUC twice normal.
- Patients with hepatic disease (cirrhosis) have ~ 47% increase in  $C_{max}$  and ~ 84% increase in AUC.

Sildenafil enhances erectile function only with sexual stimulation. Effect as measured by penile plethysmography is present 1 to 4 hours post dose. (Note: 2 hours is better than 4 hours.) Benefit can last up to 8 hours.

**CLINICAL TRIALS:** NDA included > 3,000 males (age 19-87 years) in 21 trials up to 6 months in duration. The average duration of erectile dysfunction in these patients was 5 years and the etiology of erectile dysfunction included (organic, psychogenic and mixed). Erectile function was assessed utilizing the International Index of Erectile Dysfunction (IIEF).

1. Ability to achieve erections sufficient for sexual intercourse.
2. Maintenance of erection after penetration (graded on a scale of 0-5, 0 = none; 1 = never or almost never; 2 = few; 3 = sometimes; 4 = most of the time; 5 = always).

1,797 patients - baseline median score = 2, treated with sildenafil or placebo for 12-24 weeks.

- 58% of patients had organic causes including DM (excluded spinal cord injury)
- 17% psychogenic
- 24% mixed organic and psychogenic
- dose related improvement in duration and rigidity of erection with sexual stimulation
- 24% placebo; 63% 25 mg; 74% 50 mg and 82% 100 mg

268 patients with diabetes mellitus and erectile dysfunction

- 57% of patients improved vs. 10% with placebo (48% of sexual intercourse attempts were successful with sildenafil vs. 12% with placebo).

178 patients with spinal cord injury and erectile dysfunction

- 83% of patients improved vs. 12% with placebo (59% of sexual intercourse attempts were successful vs. 13% with placebo.) Higher response rates in patients with partial lesions.

Radical prostatectomy patients

- 43% improved vs. 15% with placebo

328 patients with psychogenic erectile dysfunction

- 84% improved vs. 26% with placebo

Package insert states that sildenafil is also effective in patients with drug-induced erectile dysfunction (ie, antihypertensives, antidepressants and antipsychotics)

#### **ADVERSE EFFECTS:**

- mild headache 16%
- flushing 11%
- indigestion 7%
- runny nose 7%
- transient visual disturbance\* 3%

\* includes increased brightness, blue haze and loss of blue-green color vision, but **no** loss of visual acuity, night vision or increase in intraocular pressure.

- **no** episodes of priapism
- blood pressure reduced ~ 8-9 mm Hg systolic and 5-6 diastolic

**CONTRAINDICATION!** Do not use in any patient taking any formulation of nitrates!

Severe drop in blood pressure (up to 30-40 mm Hg) and fainting have been reported. No data concerning use in combination with therapies for erectile dysfunction.

**DRUG INTERACTIONS:** Metabolized by CYP 3A4, therefore consider initiating therapy with 25 mg in patients on 3A4 inhibitors (ie, erythromycin, clarithromycin, mebefradil, cimetidine, itradonazole, ketoconazole, grapefruit, etc.)

**DOSAGE/COST:** For most patients, consider starting with the 50 mg tablet. Dosage can be increased to 100 mg or decreased to 25 mg depending upon the patient's response. Recommended frequency is no more than once a day.

Doses of 200 mg are not more effective than 100 mg and doses up to 800 mg have been given without significant safety concerns.

25 mg tabs

50 mg tabs

100 mg tabs

\$8.75/tab AWP

**USE OF SILDENAFIL (VIAGRA) IN PATIENTS WITH CARDIOVASCULAR DISEASE – ACC/AHA EXPERT CONSENSUS DOCUMENT  
(J Am Coll Cardiol 1999;33:273-82)**

**Use of Viagra in Patients at Clinical Risk from CV effects-**

- Absolutely contraindicated in patients taking any form of nitrate including amyl nitrate i.e. “poppers” (potential for life threatening hypotension).
- Sildenafil is contraindicated in any patient who has taken a nitrate within the last 24 hours.
- Patients with stable coronary disease, not taking a long acting nitrate, and does not appear to need nitrates on a consistent basis, the physician and patient should carefully weigh the risks and benefits of sildenafil treatment.
- Potentially hazardous
  - Patients with myocardial ischemia not on nitrates
  - Patients who can achieve at least 5 to 6 METS on an exercise tolerance test are potentially at low risk from coitus with a familiar partner, in familiar settings, without the added stress of a heavy meal or alcohol.
  - Patients with CHF and borderline low blood pressure or low volume status.
  - Patients on multi-drug regimens for blood pressure.
  - Patients on drugs which can interact with the metabolism of Viagra (i.e. CYP 3A4 inhibitors) or enhance its elimination half-life.

**Management of Acute Ischemic Syndromes in Patients on Viagra-**

- Try to establish the time of the last dose of Viagra. Avoid nitrates in the first 24 hours after the last dose.
- Support BP with fluids and alpha-adrenergic agonists if needed.
- Use beta-blockers.
- Patients with an acute MI can be treated with all therapies except nitrates (i.e. thrombolytics, angioplasty, etc.).
- Patients with unstable angina can also be treated with any therapy except nitrates ( i.e. ASA, heparin, beta-blockers, CCB's, narcotics, etc.).

**Treatment of the Hypotensive Patient with Inadvertent Viagra and Nitrate Combination-**

- Discontinue nitrates and or nitroprusside.
- Aggressive fluid resuscitation.
- IV alpha-adrenergic agonist (phenylephrine – Neosynephrine).
- Cautious use of an alpha and beta adrenergic agonist ( norepinephrine)
  - norepinephrine can exacerbate acute ischemia.
- Intraaortic balloon counterpulsation.

Note - No evidence of CV problems has been associated with Viagra and inorganic nitrates or L-arginine (the substrate from which nitric oxide is synthesized) as commonly found in food products or from environmental sources (i.e. smoking).and these compounds do not contribute to the circulating NO levels.

- Coital death is rare, with only about 0.6% of sudden death cases.
- In the laboratory setting healthy males with their usual female partner achieved an average peak heart rate of 110 bpm with the woman-on-top coitus and an average peak heart rate of 127 bpm with man-on-top coitus,
- The person at most risk is usually middle-aged and having an extramarital relations.
- Visual effects, especially at higher doses (>100mg) including transient visual abnormalities (mostly color-tinged blue-green vision, increased perception of light and blurred vision). Appears to be related to the weaker inhibiting action of sildenafil on PDE6, which regulates signal transduction pathways in the retinal photoreceptors. Viagra should be used with extreme caution if at all in patients with inherited disorders of retinal PDE6, such as retinitis pigmentosa.

## **MONTELUKAST-SINGULAIR® by Merck & Co.-1S**

**INDICATIONS:** Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and children 6 years of age and older. Zafirlukast is indicated for use in adults and children 12 years of age and older.

**CLINICAL PHARMACOLOGY:** Montelukast is a selective leukotriene receptor antagonist, like zafirlukast, which inhibits the cysteinyl leukotriene receptor (CyLT1) and is capable of preventing leukotriene (LTD<sub>4</sub>)-induced airway effects. Montelukast antagonizes LTD<sub>4</sub>-induced contractions in isolated airways, but not contractions induced by serotonin, acetylcholine, histamine or prostaglandin D<sub>2</sub>.

Montelukast produced inhibition of LTD<sub>4</sub>-induced bronchoconstriction in patients with mild asthma at oral doses of 5 mg, 20 mg, 100 mg and 250 mg administered 4 hours prior and 200 mg administered 20 hours prior to nebulized LTD<sub>4</sub> challenge.

**PHARMACOKINETICS:** Peak montelukast levels are reached within 2 to 2.5 hours after administration of the chewable tablet and 3 to 4 hours after oral administration of the 10 mg tablet. The mean oral bioavailability of the 10 mg tablets is 64%. Pharmacokinetics of the 10 mg tablets are not altered by administration with breakfast. The mean oral bioavailability of the chewable tablet is 73% when administered in the fasted state and 63% when administered with breakfast.<sup>1</sup> It is more than 99% plasma protein bound.

The mean plasma half-life is 2.7 to 5.5 hours. Montelukast is extensively metabolized primarily via the cytochrome P450 3A4 and 2C9 isozymes.

The pharmacokinetics of montelukast in the elderly do not differ from those in younger patients, although the plasma half-life is slightly prolonged. Pharmacokinetics in adolescents ( $\geq 15$  years of age) administered the 10 mg tablets and children 6 to 14 years of age administered the chewable tablets are similar to those of administration of the 10 mg tablets in adults. Metabolism is reduced in patients with mild-to-moderate hepatic impairment and evidence of cirrhosis, resulting in an approximately 40% increase in the AUC.

### **COMPARATIVE EFFICACY:**

#### *Montelukast - Clinical Trials Using the FDA-Approved Doses*

The efficacy of montelukast 10 mg once daily for the chronic treatment of asthma in adolescents and adults 15 years of age and older was evaluated in two large 12-week, double-blind, placebo controlled trials enrolling 1,576 patients. Patients had mild-to-moderate asthma and required approximately five puffs of an inhaled beta-agonist per day on an "as-needed" basis. FEV<sub>1</sub> was increased to a greater extent in montelukast-treated patients. In addition, montelukast-treated patients experienced a greater

reduction in daytime asthma symptoms, beta-agonist use and nocturnal awakenings, and an increase in morning and evening peak expiratory flow rates compared to placebo-treated patients. "As-needed" beta-agonist use was reduced 26.1% from baseline compared to a 4.6% reduction in the placebo group. Treatment effects were achieved with the first dose and maintained throughout the treatment period. In one of the studies, beclomethasone dipropionate 200 mcg twice daily with a spacer was compared with montelukast. Beclomethasone-treated patients experienced a greater improvement in FEV<sub>1</sub> over baseline (p<0.001) and a greater reduction in daytime symptom scores (p<0.001).

Montelukast was also evaluated in pediatric patients 6 to 14 years of age in a double-blind, placebo controlled study enrolling 336 patients using inhaled beta-agonists on an "as-needed" basis. Patients received either placebo or montelukast 5 mg once daily as a chewable tablet for 8 weeks. Montelukast produced greater improvement in FEV<sub>1</sub> than placebo. "As-needed" beta-agonist use was reduced 11.7% in the montelukast group compared to an 8.2% increase in the placebo group. Montelukast also reduced the percent of days asthma exacerbations occurred and improved global asthma evaluations.

Asthma patients with a documented aspirin sensitivity who were receiving inhaled or oral corticosteroids had better improvements in their asthma control following the addition of montelukast.

In patients with exercise-induced exacerbation of asthma, montelukast 10 mg once daily produced a reduction in mean maximal percent fall in FEV<sub>1</sub> and mean time to recovery to within 5% of the pre-exercise FEV<sub>1</sub>. Montelukast did not prevent clinical deterioration in maximal percent fall in FEV<sub>1</sub> after exercise. Similar effects were observed in pediatric patients treated with a 5 mg chewable tablet once daily. Protection against exercise-induced bronchoconstriction was evident 20 to 24 hours after administration of 10 mg, 50 mg and 100 mg doses.

#### **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:**

Montelukast is not indicated for the reversal of bronchospasm in acute asthma and should not be used to treat acute episodes of asthma, but it may be continued during acute exacerbations of asthma. It should not be used as monotherapy in patients with exercise-induced bronchospasm.

Montelukast is classified in Pregnancy Category B. No teratogenicity was observed in animal studies. Animal studies indicate montelukast is excreted in breast milk. Therefore, it should be administered with caution in nursing mothers.

**ADVERSE REACTIONS:** Like zafirlukast, montelukast is well tolerated. The most common side effects in clinical trials occurring at a greater frequency than with placebo included headache, respiratory infections, dyspepsia, abdominal pain and rash. Hepatic transaminase elevations have been reported during montelukast therapy, but not at an incidence greater than observed with placebo.

**DRUG INTERACTIONS:** Unlike zafirlukast, montelukast does not inhibit any of the cytochrome P450 isozymes. No interactions with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin or warfarin were observed in drug interaction studies. Phenobarbital reduced the AUC of montelukast by approximately 40%. Similar interactions are anticipated with other cytochrome P450 enzyme inducers including rifampin.

**DOSING:** The dosage for adults and adolescents  $\geq 15$  years of age is 10 mg once daily in the evening. The dosage for pediatric patients 6 to 14 years of age is 5 mg once daily in the evening. Montelukast can be administered without regard to meals. The relative efficacy of morning administration compared to evening dosing has not been evaluated. The 10 mg tablet is recommended for patients  $\geq 15$  years of age, while the 5 mg chewable tablets are recommended for children 6 to 14 years of age.

**PRODUCT AVAILABILITY:** It is available as 5 mg cherry-flavored chewable tablets and 10 mg film-coated tablets.

<b>COST:</b>	5 mg chew tabs	\$2.23/tab	AWP
	10 mg tabs	\$2.23/tab	AWP

**CONCLUSION:** Like zafirlukast, montelukast reduces bronchoconstriction via activity as a leukotriene antagonist and should not be used to relieve an acute asthma episode. No direct comparative studies have been conducted with montelukast and zafirlukast. Both drugs provide better chronic asthma management than placebo when used alone or in combination with inhaled corticosteroids. Montelukast offers an alternative to zafirlukast, with the advantages of once-daily administration, administration without regard to meals and has fewer drug interactions. However, a number of these patients will be already taking a product (eg, beta agonist, corticosteroid) that requires more than once-daily dosing so the decrease in dosing frequency may not be a major advantage.