

## LEVALBUTEROL (R-albuterol) - XOPENEX™ (Sepracor, Inc.)

**INDICATIONS:** Levalbuterol is approved for the treatment of asthma.

**CLINICAL PHARMACOLOGY:** All marketed  $\beta_2$  agonists are racemic mixtures. Albuterol is a racemic mixture of R-albuterol and S-albuterol. The R-albuterol contributes to bronchodilatation, while the S-albuterol has been considered "inactive." The peak effects of R,S-albuterol and R-albuterol are similar. The equivalent inhaled dose of R-albuterol is 1 microgram for every 2 micrograms of R,S-albuterol.

Newer evidence indicates that the S-albuterol enhances the inflammatory response, augments calcium mobilization following carbachol exposure and increases airway hyperreactivity to spasmogens and allergens. These effects from the S-albuterol decrease the effectiveness of the R-albuterol or even contribute to the tolerance/tachyphylaxis and some of the possible toxicities associated with long-term  $\beta_2$  agonist use. (See Handley DA, McCullough JR, Crowther SD, Morley J. Sympathomimetic enantiomers and asthma. *Chirality* 1998;10:262-72 for a comprehensive review on the subject of bronchodilator enantiomers and their effects on asthma.)

**PHARMACOKINETICS:** Enantiomers are not always eliminated at the same rate. Instead, they undergo stereoselective metabolism, with one enantiomer being metabolized more rapidly than the other. This process could result in more rapid elimination of the active enantiomer and slower elimination of the "inactive" or antagonist enantiomer. Such is the case with albuterol. Albuterol is metabolized by sulfate conjugation and shows stereoselective metabolism. The R-enantiomer is eliminated faster, thus the plasma concentration of the S-enantiomer is higher than the R-enantiomer within a couple of hours of administration (see Table 1). The rate of sulfate conjugation and stereoselective metabolism also varies between tissues. In the intestinal tract, stereoselective sulfation is great and results in a lower oral bioavailability of the R-albuterol compared to R,S-albuterol and S-albuterol (see Table 1).

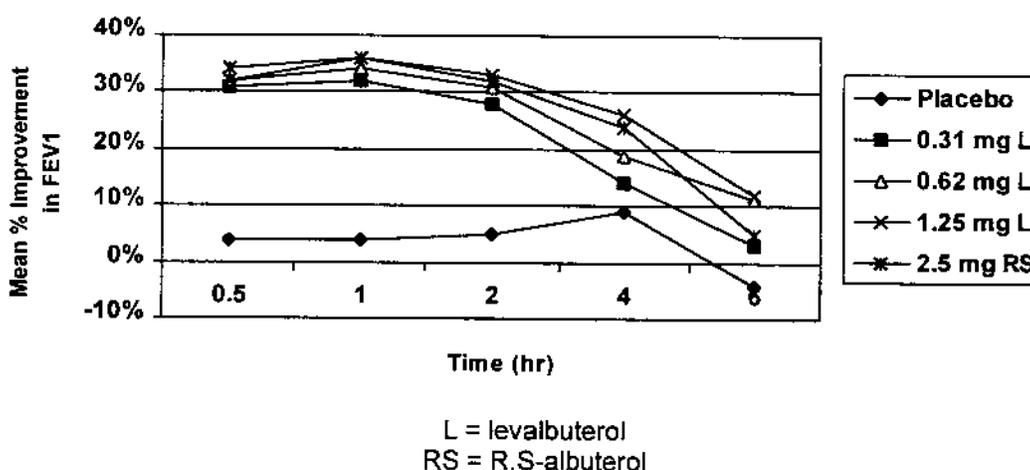
Table 1: Pharmacokinetics of Albuterol in Healthy Volunteers:

Parameter	Inhaled	Intravenous	Oral	Rectal
<i>Amount unchanged in the urine</i>				
R-albuterol	24.6%	46%	8%	20%
S-albuterol	47.4%	55%	32%	28%
<i>Systemic availability</i>				
R-albuterol			0.3	0.33
S-albuterol			0.71	0.4
<i>Renal clearance (mL/min/kg)</i>				
R-albuterol		5.3	3.1	4.5
S-albuterol		4.3	2.8	3.7
<i>Systemic clearance (mL/min/kg)</i>				
R-albuterol		10.3		
S-albuterol		6.5		
<i>Half-life (hr)</i>				
R-albuterol	5	2		
S-albuterol	7.1	2.85		
<i>Volume of distribution (L/kg)</i>				
R-albuterol		2		
S-albuterol		1.77		

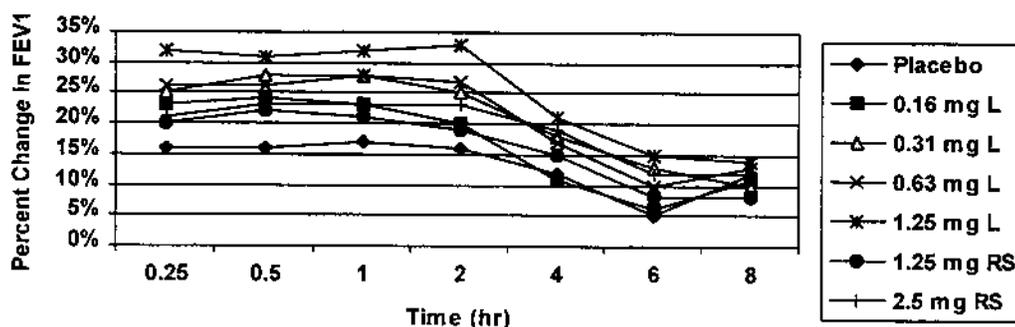
**COMPARATIVE EFFICACY:** There was a difference in the time course of the clinical effect when patients were given levalbuterol, S-albuterol or R,S-albuterol then challenged with methacholine. Within 20 minutes, S-albuterol produced a weak bronchodilatory effect, but this effect did not last long. Instead, 3 hours after S-albuterol was administered there was an increased responsiveness to the methacholine, whereas the hyperresponsiveness of the bronchi was suppressed by levalbuterol and R,S-albuterol for at least 3 hours. After 3 hours, the effectiveness of R,S-albuterol decreased and levalbuterol was still active. The difference between the R,S-albuterol and levalbuterol was a result of higher levels of S-albuterol, since levalbuterol is eliminated faster than the S-albuterol.

Twenty patients with mild-to-moderate asthma were enrolled in a single-dose, double-blind, crossover study to evaluate the effectiveness of levalbuterol. The patients were treated with 0.31 mg levalbuterol, 0.62 mg levalbuterol, 1.25 mg levalbuterol, 2.5 mg R,S-albuterol and placebo. Serial pulmonary function tests were done over 6 hours starting immediately prior to and following administration of the test drug. Each patient was treated with each drug and dose on 5 separate days. Based on pulmonary function tests, 0.62 mg levalbuterol was equivalent to 2.5 mg R,S-albuterol (see Figure 1) and had fewer side effects. Adverse effects occurred most frequently with the 1.25 mg levalbuterol and 2.5 R,S-albuterol, but the levalbuterol therapy had less effect on heart rate.

Figure 1: Mean % Improvement in FEV<sub>1</sub>:<sup>30</sup>



The safety and effectiveness of levalbuterol were also evaluated in 43 children with asthma. Each patient was treated with four of seven different treatments on different days using a single-dose crossover design. Treatment was assigned randomly to 1.25 mg R,S-albuterol, 2.5 mg R,S-albuterol, 0.16 mg levalbuterol, 0.31 mg levalbuterol, 0.63 mg levalbuterol, 1.25 mg levalbuterol or placebo. Serial pulmonary function testing was done prior to and for 8 hours after nebulization of the study drug. Thirty three of the patients (76.7%) completed all four visits; five patients were aged 3 to 5 years and 28 patients were aged 6 to 11 years. The reported results only include the percent change in FEV<sub>1</sub> for the evaluable patients in the group aged 6 to 11 years (see Figure 2). The best results were obtained with the 1.25 mg levalbuterol dose. However, the 0.31 and 0.63 mg levalbuterol and 2.5 mg R,S-albuterol doses were effective in providing adequate improvements in the FEV<sub>1</sub> for a minimum of 4 hours. Figure 2: Mean % Improvement in FEV<sub>1</sub> in Children:



L = levalbuterol  
RS = R,S-albuterol

The effectiveness of levalbuterol and R,S-albuterol was compared using a double-blind, parallel-group study design in 328 asthma patients. Patients were randomly assigned treatment with 0.63 mg levalbuterol, 1.25 mg levalbuterol, 1.25 mg R,S-albuterol, 2.5 mg R,S-albuterol or placebo. The drug was administered by nebulization three times a day for 4 weeks. Pulmonary function tests were conducted after the first dose and after the second and fourth week of therapy. The improvement in FEV<sub>1</sub> with 0.63 mg levalbuterol was equivalent to 2.5 mg R,S-albuterol. The greatest effect on FEV<sub>1</sub> was achieved with the 1.25 mg levalbuterol. Both drugs were useful in controlling asthma symptoms, but the levalbuterol therapy was associated with fewer side effects and less effect on heart rate, serum potassium and glucose.

Preliminary data from a clinical study enrolling 328 patients with asthma indicate that levalbuterol was safe and effective and may be better than R,S-albuterol in the treatment of severe asthmatics. Both drugs improved the patient's FEV<sub>1</sub>, while the patients with severe asthma (FEV<sub>1</sub> < 60% predicted) had better improvement in FEV<sub>1</sub> with levalbuterol (p=0.034). Over 1 month, the patients treated with R,S-albuterol had a decrease in FEV<sub>1</sub> values, and the patients treated with levalbuterol remained stable. These effects were more pronounced in patients who were not receiving concomitant steroid therapy.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** The contraindications, warnings and precautions associated with levalbuterol therapy are the same as albuterol.

**MONITORING:** Frequency of asthma attacks should be monitored. If the frequency or severity of attacks increase, the drug regimen should be reevaluated. In addition, spirometry should be done periodically during the course of therapy, especially in patients with moderate-to-severe asthma, and the patient should be instructed on how and when to use a peak flow meter and to keep a record of these results.

**ADVERSE REACTIONS:** The adverse effects associated with levalbuterol should be similar to those reported with R,S-albuterol therapy. The risk of tachyphylaxis may be reduced with levalbuterol. However, this potential benefit is not documented in clinical trials comparing long-term levalbuterol and R,S-albuterol.

**DOSING:** The inhaled dose of levalbuterol is at least half of R,S-albuterol. The nebulized dose of levalbuterol used in the clinical trials has been 0.63 mg and 1.25 mg three times daily. Based on effects on the FEV<sub>1</sub> following nebulization, the 0.63 mg levalbuterol dose is equivalent to 2.5 mg R,S-albuterol.

**PRODUCT AVAILABILITY:** Levalbuterol was granted approvable status in July 1998. It is manufactured by Sepracor, Inc., 111 Locke Dr., Marlborough, MA 01752: (508) 481-6700.

**CONCLUSION:** Levalbuterol is as effective as R,S-albuterol in the treatment of asthma. Levalbuterol offers the patient the advantage of providing only the active enantiomer of the racemic mixture. Therefore, the drug will provide all the bronchodilator effects of albuterol with a lower risk of side effects and a possible reduction in long-term toxicity.

**CITALOPRAM HYDROBROMIDE - CELEXA™ (Forest Pharmaceutical, Inc., Parke-Davis) - 1S**

**INDICATIONS:** Citalopram is indicated for the treatment of depression. The FDA-approved indications for the selective serotonin reuptake inhibitors (SSRIs) are summarized in Table 1.

Table 1: FDA-Approved Indications:

Indication	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Bulimia Nervosa		X			
Depression	X	X		X	X
Obsessive-Compulsive Disorder		X	X	X	X
Panic Disorder				X	X

**CLINICAL PHARMACOLOGY:** Citalopram is an SSRI. It is a racemic phthalane derivative, structurally unrelated to other available SSRIs or other available antidepressants. Citalopram is more selective for serotonin activity than fluoxetine, paroxetine, sertraline and fluvoxamine. Citalopram has minimal effects on norepinephrine and dopamine reuptake. Like the other SSRIs, citalopram has a no or very low affinity for serotonergic, dopamine, adrenergic, muscarinic, cholinergic, histamine, benzodiazepine, GABA and opioid receptors.

**PHARMACOKINETICS:** Peak levels of citalopram are achieved within 4 hours after oral administration. The oral bioavailability of citalopram is 80%. Absorption is not affected by food.

The half-life of citalopram is 35 hours (ranging from 28 to 60 hours). Citalopram undergoes metabolism via N-demethylation, deamination and N-oxidation, forming demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and a deaminated propionic acid derivative, all of which are believed not to contribute to the clinical efficacy of citalopram. Demethylcitalopram is 2- to 4-fold less potent than citalopram. Overall, citalopram is at least eight times more potent than its metabolites in the inhibition of serotonin reuptake. At steady state, plasma concentrations of demethylcitalopram, the main metabolite, are half those of citalopram, while plasma concentrations of didemethylcitalopram are approximately 1/10 those of citalopram. CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram. Twelve percent of an administered dose is recovered in the urine as unchanged drug, 12% as the demethylcitalopram, 1.5% as amino metabolite and 4.3% as conjugated propionic acid metabolite. It is believed fecal elimination either from enterohepatic circulation or metabolism via other as yet unknown pathways accounts for elimination of the remaining portion of the dose. Selected pharmacokinetic parameters of the SSRIs are compared in Table 2.

Table 2: Comparative Pharmacokinetics of the SSRIs:

Parameter	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Tmax	4 h	4-8 h	3-8 h	3-8 h	4-8 h
Protein binding	80 %	95 %	80 %	95 %	98 %
T1/2 parent	35 h	4-6 d	15 h	10-21 h	26 h
Active metabolite(s)*	no	yes	no	no	weak
T1/2 active metabolite	--	4-16 d	--	--	62-104 h

\* clinically important active metabolites

In elderly depressed patients, steady-state citalopram concentrations have been up to four times higher than expected from data in younger patients and healthy volunteers, while half-life has been prolonged and clearance reduced. In a multiple-dose study, the citalopram AUC and half-life were increased by 23% and 30%, respectively, in the elderly. The 20 mg dose is recommended for elderly patients.

In patients with hepatic dysfunction, citalopram clearance was reduced by 37% and half-life was doubled

compared to normal subjects. The 20 mg dose is recommended for patients with hepatic impairment. Compared to normal subjects, citalopram clearance was reduced by 17% in patients with mild-to-moderate renal dysfunction. No dosage adjustment is recommended for that patient population. There is no information on the pharmacokinetics of citalopram in patients with severe renal impairment (CrCl < 20 mL/min).

#### **EFFICACY:**

**Depression:** The efficacy of citalopram was evaluated in two placebo controlled studies summarized in the package literature. In the first study, citalopram doses of 10, 20, 40 or 60 mg/day were administered for 6 weeks to outpatients with major depression. The 40 and 60 mg doses were effective as assessed by the Hamilton Rating Scale for Depression (HAM-D) total score, the HAM-D depressed mood item, the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) Severity scale. The 60 mg dose was not more effective than the 40 mg dose. In the second study, patients were titrated from 20 mg/day to the maximum tolerated dose or a maximum dose of 80 mg/day. Greater improvements were observed in citalopram-treated patients on the HAM-D total score, HAM-D depressed mood item and the CGI Severity score.

The efficacy of citalopram was also compared with placebo in 94 elderly (65 years or older) depressed patients, some of whom had concomitant dementia. Patients were treated with either citalopram or placebo administered once daily in the afternoon. Citalopram therapy was initiated with 10 mg daily for 2 days, then 20 mg daily for 2 weeks, after which the dose could be reduced or increased as needed. Improvement in HAM-D, MADRS and CGI scores was greater in the citalopram-treated patients, although improvement was observed in both treatment groups. Some aspects of the ratings on the Gottfries-Brane-Steen dementia rating scale also showed significantly greater improvement in cognitive and emotional functioning in the citalopram-treated patients. Improvement in emotional bluntness, confusion, irritability, anxiety, fear/panic, depressed mood and restlessness was observed in another group of patients with moderate Alzheimer's Disease or senile dementia of the Alzheimer type without concomitant depression who received citalopram 10 to 30 mg once daily. Similar effects were not observed in a group of placebo-treated patients or in a group of citalopram-treated patients with vascular dementia. Irritability, depressed mood, anxiety, restlessness and fear-panic were reduced in elderly patients with emotional disturbances with or without dementia treated with citalopram 20 to 40 mg daily. Improvement was also reported with citalopram 10 to 20 mg daily in patients with dementia and behavioral disturbances. In other studies, citalopram was reported significantly more effective than placebo in the treatment of poststroke pathological crying and poststroke depression.

**Neuropathy:** Citalopram 40 mg administered once daily in the evening was more effective than placebo in a double-blind, crossover study evaluating 15 patients with diabetic peripheral neuropathy. Symptoms of neuropathy improved during citalopram therapy as measured by observer- and self-rating. However, in comparison to results obtained from an earlier study with imipramine, the investigators concluded citalopram appeared less effective.

**Alcoholism:** In studies enrolling alcohol-dependent individuals, citalopram 20 to 40 mg once daily decreased the number of daily alcoholic drinks; increased percentage of days of abstinence and decreased interest, desire, craving and liking for alcohol.

#### **COMPARATIVE EFFICACY:**

**Depression:** The efficacy and safety of citalopram and sertraline were compared in a double-blind study enrolling 400 patients with major depression. Patients were treated with either sertraline 50 to 150 mg/day or citalopram 20 to 60 mg/day for 24 weeks. Sertraline therapy was initiated at a dose of 50 mg/day, and citalopram was initiated at the dose of 20 mg/day. The dosage could be increased if significant clinical improvement was not observed after 4 weeks. Three hundred eight patients completed 24 weeks of therapy. Mean doses at week-24 were 82.4 mg/day in the sertraline group and 33.9 mg/day in the citalopram group. Significant improvement from 2 weeks on was observed in both treatment groups based on MADRS and CGI-severity scores. Response was observed in 69.5% of sertraline-

treated patients and 68% of citalopram-treated patients at week-12, and in 75.5% of sertraline-treated patients and 81% of citalopram-treated patients at week-24. Efficacy and tolerability were comparable in the two treatment groups. The most common side effects observed in both treatment groups were nausea, diarrhea, increased sweating, dry mouth, headache and sexual dysfunction.

Citalopram was also compared with fluoxetine in the treatment of major depression. In a double-blind study citalopram 20 mg and fluoxetine 20 mg for 8 weeks were compared in 357 patients with unipolar major depression. Significant clinical improvement was observed in both treatment groups based on HAMD, MADRS and CGI scores. Overall efficacy and tolerability were comparable, although the onset of citalopram appeared more rapid with assessments favoring citalopram at the 2-week evaluation.

The efficacy and safety of citalopram and amitriptyline were compared in two double-blind studies. In one study, patients with major depressive illness were treated with either citalopram (24 patients) or amitriptyline (20 patients) administered once daily in the evening for 6 weeks. Patients received either 10 mg citalopram tablets or 37.5 mg amitriptyline tablets, and took two tablets at night for the first 3 days, four tablets at night until the end of the third week and three to six tablets at night for the remainder of the study. Average doses in the sixth week were 46 mg of citalopram and 148 mg of amitriptyline. Significant improvement from 7 days on was observed in both treatment groups based on the Newcastle Scale, the HAM-D, MADRS and the Leeds Self-Rating Depression Scale. No difference in clinical improvement between the two treatment groups was observed. However, side effects were much more common in the amitriptyline-treated patients, primarily due to the incidence of anticholinergic side effects.<sup>32</sup> In the other study comparing citalopram and amitriptyline, 43 patients were treated with either citalopram (23 patients) or amitriptyline (20 patients) administered once a day in the evening for at least 3 weeks. Patients were given tablets containing either citalopram 10 mg or amitriptyline 37.5 mg, taking four tablets a day for the first 2 weeks with an allowed dose increase to five to six tablets a day if needed for the remainder of the study. After 1 week of therapy and continuing through the 6-week study, improvement was observed in both treatment groups, with no difference identified between the treatments based on assessment of MADRS scores. As in the other study, side effects occurred significantly less often in the citalopram-treated patients. The effectiveness of citalopram is comparable to imipramine, but with greater tolerability.

**Panic disorder:** Citalopram was compared with clomipramine in a placebo controlled study enrolling 475 patients with panic disorder, with or without agoraphobia. Patients were treated with placebo, citalopram 10 to 15 mg/day, citalopram 20 to 30 mg/day, citalopram 40 to 60 mg/day or clomipramine 60 to 90 mg/day for 8 weeks. Treatment with citalopram 20 to 30 mg, citalopram 40 to 60 mg and clomipramine were more effective than placebo. Based on the number of patients free of symptoms, the greatest efficacy was observed in the patients treated with citalopram 20 to 30 mg/day. Overall, citalopram and clomipramine offered similar efficacy and tolerability.

**Alcoholism:** In a comparative study with fluvoxamine 150 mg/day, citalopram 20 mg/day had a greater effect on reducing craving. Both therapies showed a greater rate of continuous abstinence compared to cognitive-behavioral therapy alone, but only citalopram showed an effect on craving throughout the 16-week trial.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Citalopram is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in *Celexa*. Concomitant use of citalopram in patients taking monoamine oxidase inhibitors is also contraindicated.

Adverse effects on embryo/fetal and postnatal development, including teratogenicity, have been observed with citalopram in animal studies.

Citalopram is excreted in human breast milk, and small amounts of citalopram and demethylcitalopram have been detected in the serum of a breast-fed infant. Infants may experience excessive somnolence, decreased feeding and weight loss in association with breast feeding from a citalopram-treated mother. The relative dose to the infant based on excretion in the breast milk is comparable to that observed with fluoxetine and greater than that observed with paroxetine, sertraline and fluvoxamine.

Safety and effectiveness in pediatric patients have not been established.

**ADVERSE REACTIONS:** The most common adverse reactions reported during citalopram therapy have included dry mouth, nausea, somnolence, insomnia, increased sweating, tremor, diarrhea and sexual dysfunction. The incidence of fatigue, impotence, insomnia, increased sweating, somnolence and yawning increased with increasing doses over the range of 10 to 60 mg. In general, the side effects are similar to those occurring with the other SSRIs. Compared to tricyclic antidepressants, citalopram is associated with a higher incidence of nausea and sexual dysfunction. A comparative trial found sertraline produced less sexual dysfunction than citalopram.

Postmarketing reports from Europe of citalopram overdoses have included 12 fatalities, 10 in combination with other drugs and/or alcohol and two with citalopram alone (3,920 mg and 2,800 mg). Non-fatal overdoses of up to 6,000 mg have also been reported. Symptoms most commonly accompanying citalopram overdose, alone or in combination with other drugs, included dizziness, sweating, nausea, vomiting, tremor, somnolence and sinus tachycardia. One hundred fifty-nine case reports of citalopram overdose received from Swedish hospitals in 1995 and 1996 have been summarized and reviewed. At doses below 600 mg, symptoms were described as mild (nausea, dizziness, tachycardia, tremor, drowsiness and somnolence), while doses above 600 mg caused ECG abnormalities and convulsions in some patients. Doses greater than 1,900 mg caused ECG abnormalities and convulsions in all patients.

**DRUG INTERACTIONS:** Citalopram does not inhibit CYP3A4, but it is a weak inhibitor of CYP1A2, CYP2D6 and CYP2C19. These effects are not clinically significant, but sufficient data to assess the impact are not available.

Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin) and CYP2C19 (eg, omeprazole) may reduce the clearance of citalopram. Drugs that inhibit CYP2D6 do not affect citalopram levels. Administration with cimetidine resulted in increased citalopram levels. Dosage adjustments are not necessary when these agents are administered concomitantly.

Citalopram is a weak inhibitor of cytochrome P450IID6, and as such may alter concentrations of tricyclic antidepressants. Citalopram has been used concomitantly with amitriptyline without increasing amitriptyline or nortriptyline concentrations; however, citalopram has resulted in an approximately 50% increase in single-dose AUC of desipramine after coadministration of citalopram and imipramine. Administration with metoprolol resulted in a two-fold increase in metoprolol levels.

Coadministration of citalopram and lithium resulted in no changes in the pharmacokinetics of either medication. Monitoring of lithium levels is recommended, however. Also, because lithium may enhance the serotonergic effects of citalopram, these agents should be used concomitantly with caution. Lithium augmentation of citalopram therapy has been used in the treatment of therapy-resistant depression. Fluvoxamine increases citalopram levels, particularly levels of the more active S-citalopram, via inhibition of CYP2C19, CYP2D6 and CYP3A4. This has been used therapeutically to augment citalopram therapy in nonresponders, but it also results in increased side effects.

Pharmacokinetic interactions with digoxin and warfarin have not been observed.

Ethanol effects do not appear to be enhanced or potentiated by citalopram; however, use of alcohol by depressed patients taking citalopram is not recommended.

**RECOMMENDED MONITORING:** As with the other SSRIs, plasma concentrations of citalopram have not correlated well with clinical effects.

**DOSING:** Citalopram therapy should be initiated with a dose of 20 mg once daily. Most patients will require an increase to a dose of 40 mg once daily. Dose increases should occur in increments of 20 mg at intervals of no less than 1 week. The dose may be increased up to 60 mg/day; however, no advantage of this dose over the 40 mg dose has been observed. Citalopram should be administered once daily, in the morning or evening, with or without food.

For most elderly patients and patients with hepatic impairment, the 20 mg dose is recommended, with

titration to 40 mg/day only in those patients not responding to 20 mg.

**PRODUCT AVAILABILITY:** Citalopram received FDA approval in July 1998. Citalopram has been available in Denmark since 1989 and is available in at least 30 countries. It is available as 20 mg and 40 mg film-coated, scored tablets. The available dosage forms of the SSRIs are summarized in Table 4.

Cost 20mg tablets (scored) \$2.02 AWP  
40mg tablets (scored) \$2.10 AWP

Table 4: Available Dosage Forms:

	<b>Citalopram</b>	<b>Fluoxetine</b>	<b>Fluvoxamine</b>	<b>Paroxetine</b>	<b>Sertraline</b>
Strengths	20 mg, 40 mg	10 mg, 20 mg, 20 mg/5 mL	50 mg, 100 mg	10 mg, 20 mg, 30 mg, 40 mg	50 mg, 100 mg
Capsule/Tablet	Tablet	Capsule	Tablet	Tablet	Tablet
Scored	Yes	NA	Yes	No	Yes
Liquid Dosage Form	No	Yes	No	No	No

**CONCLUSION:** Citalopram is an effective antidepressant, with efficacy and tolerability comparable to the other SSRIs. Only limited information on its use in obsessive-compulsive disorder and panic disorder is available, and at this time its use cannot be recommended for these indications.

## OXYBUTYNYN CHLORIDE EXTENDED-RELEASE TABLETS - DITROPAN XL (Alza Corp)

**INDICATIONS:** Oxybutynin controlled-release tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.<sup>1</sup> This is the same as tolterodine and is similar to the conventional oxybutynin therapy (immediate-release or non-extended-release formulation).

**CLINICAL PHARMACOLOGY:** Urinary incontinence increases with age and occurs in 5% to 10% of the adult population. Urinary incontinence can be divided into several different types (eg, urge, stress, mixed, overflow and functional). Urge incontinence is one type and represents the involuntary loss of urine associated with an abrupt and strong, often uncontrollable, desire to void. The urge is caused by involuntary detrusor contractions that occur during the filling phase of the bladder. The terms detrusor instability and overactive bladder are often interchanged. The presenting symptoms are urge incontinence, urgency and frequency. Treatment for urge incontinence has generally consisted of an anticholinergic/antimuscarinic agent (eg, propantheline, oxybutynin, tolterodine). Other drugs that have been used are estrogen and phenylpropanolamine. Other methods have included behavior techniques and adult diapers or pads. While propantheline and oxybutynin are often effective, their use is sometimes limited by dose-related antimuscarinic side effects (eg, dry mouth). The use of a sustained-release formulation is associated with less dry mouth.

Oxybutynin is an antispasmodic with anticholinergic, analgesic and local anesthetic properties. Its main metabolite, N-desethyloxybutynin, also has muscarinic receptor blocking activity. Oxybutynin has a direct antispasmodic effect on smooth muscle, including bladder smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. It was previously available only in an immediate-release tablet formulation that required administration from two to four times daily in the treatment of urge incontinence. The *Ditropan*<sup>7</sup> XL controlled-release formulation (OROS<sup>7</sup> Osmotic Drug Delivery system) allows for administration once daily.

Tolterodine and its 5-hydroxymethyl metabolite (PNU-200577) are muscarinic receptor antagonists. The parent drug and major pharmacologically active metabolite are equipotent in decreasing bladder contractions. Both agents (tolterodine and its metabolite) had more specificity for the M2 receptor, found in the bladder of the anesthetized cat, than oxybutynin. Oxybutynin exhibits a ten-fold higher selectivity for M3 over M2 receptors. Therefore, oxybutynin acts directly on the primary component that controls detrusor contraction, the M3 receptor. However, the clinical relevance of these findings has not been established. Additionally, *in vivo*, a selectivity for M3 over M2 receptors is not necessary for an effective inhibition of bladder contraction.

**PHARMACOKINETICS:** Peak plasma concentrations, following oral administration of the OROS oxybutynin, occur within 6 to 13 hours. This controlled-release formulation continues to maintain adequate plasma oxybutynin concentrations throughout the 24-hour dosing period. Steady-state oxybutynin levels are reached within 3 days of repeated once-daily administration.

The relative bioavailability of R- and S-oxybutynin from the OROS controlled-release formulation are 156% and 187%, respectively, compared to the immediate-release formulation. Plasma concentrations of the R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with the immediate-release formulation. The rate and extent of absorption and metabolism of oxybutynin are not affected by administration with food. The release of oxybutynin from the OROS controlled-release formulation is also independent of pH or gastrointestinal motility.

Oxybutynin undergoes extensive first-pass hepatic metabolism primarily by CYP3A4 found in the liver and gut wall. The major metabolite, phenylcyclohexylglycolic acid is inactive; however, the N-desethyloxybutynin metabolite has activity similar to that of oxybutynin. The elimination of oxybutynin is biphasic. Pharmacokinetic parameters of oxybutynin administered as immediate-release and controlled-release tablets and tolterodine are compared in Table 1.

Table 1: Pharmacokinetics of Oxybutynin and Tolterodine:

Treatment	% Reduction in Urge Episodes	% Patients Continent at Endpoint	% Patients Experiencing Moderate-to-Severe Dry Mouth
Oxybutynin XL (n=34)	90	50	*
Oxybutynin IR (n=32)	77	28	
Placebo (n=16)	49	13	
Oxybutynin XL (n=53)	84	41	25
Oxybutynin IR (n=52)	88	40	46
Oxybutynin XL (n=111)	83	42	17
Oxybutynin IR (n=115)	76	34	26
Oxybutynin XL (n=256)	83	44	23

\* Data not cited.

A (S)-oxybutynin product is currently under development by Sepracor. In a phase II study enrolling 186 patients, (S)-oxybutynin was reported to reduce urinary frequency and incontinence episodes to a greater extent than placebo. Moderate-to-severe dry mouth was reported in 14% to 16% of patients. The antimuscarinic activity of oxybutynin resides predominantly in the R-isomer.

Other urinary incontinence drugs that are in Phase II development at this time are duloxetine (Lilly) and darifenacin (Pfizer).

#### CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:

The OROS formulation uses biologically inert components in the tablet thus the insoluble shell will be eliminated in the feces intact.<sup>1</sup> Patients should be instructed that they may see this in their feces and this does not mean the drug was not absorbed. Patients should also be informed that the drug may contribute or cause heat prostration, drowsiness, blurred vision, drowsiness with alcohol and not to chew, divide or crush the tablets.<sup>1</sup>

**ADVERSE REACTIONS:** The most common side effects reported with therapy with oxybutynin controlled release are anticholinergic in nature and include dry mouth (59%; with 24% having moderate-to-severe dryness), constipation (13%) and somnolence (11%). Other adverse effects occurring in more than 2% of patients treated with oxybutynin controlled release in clinical trials included headache, asthenia, pain, abdominal pain, dry nasal and sinus membranes, accidental injury, back pain, flu syndrome, palpitations, hypertension, vasodilation, nausea, diarrhea, dyspepsia, flatulence, gastroesophageal reflux, arthritis, dizziness, insomnia, nervousness, confusion, rhinitis, upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis, dry skin, rash, blurred vision, dry eyes, urinary retention, impaired urination, urinary tract infection, increase post void residual volume and cystitis. Only 1% of patients treated with oxybutynin controlled release discontinued due to dry mouth. Additionally, with tolterodine doses of 1 mg twice daily, the incidence of cardiovascular adverse events was reported as 12.4% versus 6.3% for oxybutynin 5 mg three times daily.

The overall incidence of dry mouth reported in trials with immediate-release oxybutynin has been up to 88%. In a meta-analysis of three studies comparing OROS oxybutynin controlled-release and oxybutynin immediate-release formulations, the incidence of moderate-to-severe dry mouth was lower in the controlled-release group (23.7% vs 34.2%,  $p=0.015$ ), as was the overall incidence of dry mouth (57.1% vs 69.3%,  $p=0.005$ ). Additionally, when tolterodine was administered at a dose of 4 mg twice daily, the incidence of mild-to-moderate dry mouth was reported by up to 56% of patients along with an increase in the incidence of urinary retention.

**MONITORING:** No special monitoring is required with oxybutynin therapy. However, patients treated with antimuscarinic agents should be monitored for improvement in urinary frequency, urgency or urge incontinence and the development of intolerable side effects.

**DRUG INTERACTIONS:** As with all antimuscarinic agents, the concomitant administration of oxybutynin with other anticholinergic agents or other agents which produce dry mouth, constipation, drowsiness or other anticholinergic effects may increase the incidence of such effects. No specific drug interaction studies have been performed.

Medications that induce or inhibit the CYP3A4 isozyme may alter oxybutynin pharmacokinetics and potentially reduce product efficacy or increase toxicity.

Oxybutynin should be used with caution in patients receiving concomitant medications that can cause or exacerbate esophagitis.

**DOSING:** Patients already taking immediate-release oxybutynin can be switched to oxybutynin controlled release at the closest equivalent total daily dose, with further dosage adjustments made as needed. Oxybutynin controlled release tablets should be swallowed whole, without dividing, crushing or chewing. The usual adult starting dose is 5 mg once daily. The dosage may be adjusted in 5 mg increments at approximately weekly intervals up to a maximum of 30 mg/day. The recommended dosages of oxybutynin and tolterodine are summarized in Table 4.

Table 4: Dosing of Immediate- and Controlled-Release Oxybutynin and Tolterodine:

	Oxybutynin	Oxybutynin XL	Tolterodine
Dose	5 mg two to three times daily	5 mg once daily initially, dose titrated in 5 mg increments weekly as needed	2 mg twice daily (1 mg twice daily in patients with hepatic dysfunction and patients receiving CYP3A4 inhibitors)
Max. dose	5 mg four times daily	30 mg/day	
Children >5	5 mg two times daily	Safety and effectiveness not established	Safety and effectiveness not established
Max. pediatric dose	5 mg three times daily	--	--

**PRODUCT AVAILABILITY:** *Ditropan XL* received FDA approval in December 1998. The available dosage forms for oxybutynin and tolterodine are summarized in Table 5.

Table 5: Oxybutynin, Oxybutynin XL and Tolterodine Product Availability:

Agent	Dosage Form	Strengths	Package Sizes	AWP
Oxybutynin	Tablets,	5 mg,	100, 1000 count bottles,	\$17.49 100 count 5

(Ditropan, generics)	Syrup	5 mg/5 mL	100 count unit dose, 16 ounce bottles	mg
Oxybutynin XL	Tablets	5 mg, 10 mg	100 count bottles	\$228.00 100 count 10mg, \$204.00 100 count 5mg
Tolterodine	Tablets	1 mg, 2 mg	60, 500 count bottles, 140 count unit dose	\$59.10 60 count 2 mg

**CONCLUSION:** Oxybutynin and tolterodine are equally effective in the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence. Therapy with either agent is generally associated with adverse effects, but the tolterodine therapy is better tolerated and requires less frequent dosing than immediate-release oxybutynin (two times daily vs three times daily). Oxybutynin controlled release requires only once-daily administration and has comparable efficacy and a lower incidence of adverse effects than immediate-release oxybutynin. Studies comparing oxybutynin controlled release and tolterodine are needed. Some prescribers and provider organizations may choose to use oxybutynin immediate release before the controlled-release formulation or tolterodine because of cost. However, a number of the patients will require discontinuation of therapy with oxybutynin immediate release because of side effects. In those cases, oxybutynin controlled release or tolterodine are reasonable alternatives.

## CELECOXIB - CELEBREX™ (Searle/Pfizer)

Celecoxib is the first of a new class of selective cyclooxygenase (COX-2) selective nonsteroidal antiinflammatory agents with antiinflammatory, analgesic and antipyretic activity similar to the other marketed NSAIDs but with the potential for significantly fewer adverse effects, especially on the gastric mucosa and the platelets.

**INDICATIONS:** Celecoxib (SC-58635) has been approved for the treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). The manufacturer will also be seeking approval for the treatment of acute pain.

**CLINICAL PHARMACOLOGY:** Nonsteroidal anti-inflammatory agents (NSAIDs) work by blocking cyclooxygenase (COX-1 and -2), thus they are useful in preventing the production of inflammatory prostaglandins and treating pain. Celecoxib and rofecoxib are COX-2 selective inhibitors (see Table 1). COX-2 activity is rapidly upregulated during inflammation, pain conditions and may be involved in pathogenesis of some malignancies.

Table 1: In Vitro COX-1 and -2 Selectivity Using a Prostaglandin ELISA Assay:

Drug	Half-Maximal Inhibition (IC <sub>50</sub> )	
	hCOX-1	hCOX-2
Indomethacin	0.08	0.5
Mefenamate	3.6	122
Diclofenac	0.02	0.01
Flurbiprofen	0.4	2.7
Naproxen	21	88
DUP-697	0.9	0.001
NS-398	>100	0.05
Celecoxib	>100	0.04
SC-236	17	0.005

hCOX-1 & -2: wild-type enzyme

The potential advantage of using a COX-2 selective agent is the benefit of decreasing the production of the inflammatory prostaglandins produced by COX-2 without decreasing the production of the prostaglandins produced by COX-1 which are important in other body functions (see Tables 2 and 3). In vitro studies show that celecoxib has a 375-fold selectivity for COX-2. This type of enzyme selectivity would allow this agent to control the inflammation and pain, but not cause some of the toxicities associated with NSAID therapy.

Table 2: Difference in Pharmacologic Activity of NSAIDs and COX-2 Inhibitors:

Property	NSAIDs	COX-2 Inhibitors
Anti-inflammatory	X	X
Analgesic	X	X
Platelet dysfunction	X	
GI side effects	X	
CNS side effects	X	
Renal side effects	X	
Bronchospasm	X	

Table 3: Location of COX Enzymes:

Location	COX-1	COX-2
Gastrointestinal tract	X	
Platelets	X	
Endothelial cells	X	
Renal medullary collecting ducts and interstitium	X	
Brain		X
Renal cortex and medullary interstitial cells		X
Synovial tissue		X
Colorectal adenomas and carcinomas		X
Breast cancer		X
Head and neck cancer		X
Lung	X	
Liver	X	
Spleen	X	
Site of inflammation		X

COX-2 selective inhibitors have little effect on platelet function. In vitro data indicate that agents that inhibit COX-1 also inhibit thromboxane B<sub>2</sub> production. However, effects of the NSAIDs on thromboxane B<sub>2</sub> production varied greater depending on their affinity for the COX-1 enzyme; high affinity agents (eg, flurbiprofen, sulindac sulfide, diclofenac, indomethacin) had the greatest effect and low affinity agents (eg, etodolac, nabumetone) had the least effect.

**PHARMACOKINETICS:** after oral administration, peak celecoxib levels are reached within about 2.5 to 3.0 hours and both peak plasma levels (C<sub>max</sub>) and area under the curve (AUC) are roughly dose proportional within the usually dosage range. Administration with meals does not significantly alter the amount absorbed but may delay peak levels by 1 to 2 hours. Celecoxib may be given with meals. Celecoxib is highly protein bound (~97%), primarily to albumin. It is extensively hepatically metabolized primarily by CYP 450 2C9 to three inactive metabolites (ie they are not COX – 1 or 2 inhibitors). Concurrent use of CYP 450 2C9 inhibitors like fluconazole, Isoniazid or ticlopidine could produce abnormally high plasma levels due to reduced metabolic clearance. Fluconazole has been shown to double celecoxib plasma levels when administered at 200mg per day. Note that this potential interaction is not unique to celecoxib but is shared by most other NSAIDs (ie diclofenac, ibuprofen, Naproxen, and piroxicam). Celecoxib is eliminated primarily by hepatic metabolism with less than 3% being

excreted unchanged in the feces and urine. The elimination half-life is about 11 hours.

## **EFFICACY:**

### **Osteoarthritis**

A randomized, double-blinded, dose-ranging study enrolling 293 patients with osteoarthritis of the knee was conducted. Patients were given 40, 100 or 200 mg celecoxib or placebo twice daily for 2 weeks when the patient's knee was in a flare state. Patients were excluded if they were receiving any glucocorticoids (other than topical) within 12 weeks, an NSAID or analgesic within 2 days (except  $\leq 325$  mg/day), if they had active gastrointestinal disease, chronic or acute renal or hepatic dysfunction or a coagulation defect. The effectiveness of the agent in controlling the pain associated with the arthritis was done using a 100 mm visual analog scale (VAS) and functional capacity classification. Assessments were conducted after 1 and 2 weeks of therapy. Twenty patients withdrew from the study due to lack of effectiveness; 14% in the placebo group, 8% in the celecoxib 40 mg group, 1% in the celecoxib 100 mg group and 4% in the celecoxib 200 mg group. The mean improvements in the VAS ranged from -22.02 mm to -29.22 mm after 1 week with celecoxib compared to -12.65 mm with the placebo ( $p \leq 0.048$ ). The mean improvements ranged from -22.78 to -30.52 mm after 2 weeks with celecoxib and -15.48 mm with the placebo;  $p \leq 0.048$  except the celecoxib 40 mg dose ( $p = 0.083$ ). The patient's global assessment score indicated a preference for the celecoxib. The mean change from baseline ranged from -1.11 to -1.35 with celecoxib compared to -0.61 with placebo after 1 week ( $p \leq 0.002$ ). While after 2 weeks of therapy, the mean change in the patient's global assessment score ranged from -1.03 to -1.29 with celecoxib and -0.8 with placebo; the p-value with celecoxib 40 mg was  $\leq 0.011$ , celecoxib 100 mg was 0.174 and celecoxib 200 mg was  $\leq 0.011$ .

A randomized, double-blinded, placebo controlled, parallel-group study enrolling 1004 patients with a flare of osteoarthritis of the knee was conducted. Patients were given celecoxib 50, 100 or 200 mg, naproxen 500 mg or placebo twice daily for up to 12 weeks. The effectiveness of the agent in controlling the patient and physician global assessments, patient assessment of pain and Osteoarthritis Severity Index indicated that the 50 mg dose of celecoxib was better than placebo, but not as effective as naproxen or the higher doses of celecoxib. The celecoxib 100 and 200 mg dose and naproxen therapy were equally effective.

### **Rheumatoid Arthritis**

A randomized, double-blinded, dose-ranging study enrolling 330 patients with rheumatoid arthritis in a flare state was conducted. Patients were given 40, 200 or 400 mg celecoxib or placebo twice daily for 4 weeks. Patients were excluded if they were receiving disease-modifying antirheumatic drugs, antimalarial agents, glucocorticoids, an NSAID within 2 days (except  $\leq 325$  mg/day), any analgesics within 24 hours, if they had active gastrointestinal disease, chronic or acute renal or hepatic dysfunction or a coagulation defect. NSAIDs or analgesic could be discontinued and patients returned to the clinic when their symptoms worsened. The effectiveness of the agent in controlling the condition was done using a 100 mm visual analog scale (VAS), assessment of joint swelling, joint tenderness/pain, duration of morning stiffness, functional capacity classification and level of C-reactive protein. Assessments were conducted after 1, 2 and 4 weeks of therapy. Thirty-seven patients withdrew from the study due to lack of effectiveness; 18% with placebo, 17% with celecoxib 40

mg, 4% with celecoxib 200 mg and 6% with celecoxib 400 mg. The mean improvement in the patient's global assessment of arthritis ranged from -0.83 to -1.14 with celecoxib after 1 week, -0.69 and -1.24 after week-2 and -0.65 and -1.19 by week-4 ( $p \leq 0.001$ ). The improvement in the placebo group did not exceed -0.61 after 1, 2 or 4 weeks of therapy. The difference between placebo and celecoxib was not significant except at the end of week-1. The mean reduction in number of tender/painful joints ranged from 10 to 15 joints with celecoxib therapy at each visit, while the placebo group ranged from 7 to 10 joints. The difference between celecoxib therapy and placebo was significant ( $p < 0.005$ ) except for the celecoxib 40 mg group. The higher-dose celecoxib therapy also was better than placebo using the ACR criteria.

A double-blind, placebo controlled trial was conducted in rheumatoid arthritis patients whose condition was in flare ( $n=1149$ ). Patients were randomized to treatment with celecoxib 100, 200 or 400 mg, naproxen 500 mg or placebo twice daily for 12 weeks. All active drugs were better than placebo and all the celecoxib doses were at least as effective as the naproxen. The incidence of gastroduodenal ulcers was 6% with celecoxib 100 mg, 4% with celecoxib 200 mg, 6% with celecoxib 400 mg, 26% with naproxen and 4% with placebo.

A European study enrolled 655 rheumatoid arthritis patients using a double-blind, double-dummy, parallel-group study design. Patients were treated with either celecoxib 200 mg or sustained-release diclofenac 75 mg twice daily for up to 24 weeks. No differences were observed in the improvements in clinical parameters of the disease. Therapy was discontinued due to lack of effectiveness in 8% of those treated with celecoxib and 7% of those treated with diclofenac. The incidence of gastroduodenal ulcers was 4% with celecoxib and 15% with diclofenac ( $p=0.001$ ). The incidence of gastric ulcers was 2% and 11% ( $p=0.002$ ) and the incidence of duodenal ulcers was 2% and 7% ( $p=0.003$ ), respectively.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Celecoxib is contraindicated in patients with a history of allergic reactions to the drug or the product ingredients. Celecoxib should not be given to patients with a history of asthma, urticaria or other type of allergic reactions after taking aspirin or other NSAIDs. Since the chemical structure of celecoxib contains a benzenesulfonamide group. Celecoxib should not be given to patients with a demonstrated allergic reaction to sulfonamides.

Pregnancy category C, celecoxib had no effect on labor and parturition in rats at doses up to 100mg/kg. The effects in humans is not known. Avoid this agent as well as other NSAIDs during late stages of pregnancy as they may cause premature closure of the ductus arteriosus.

A recent issue that needs to be addressed is the potential effect of COX-2 inhibitors on the risk of vascular disease, as COX-2 appears to have a role in sustaining vascular prostacycline production. To date no human data is available to adequately evaluate this potential effect, however in the clinical trial data base there was no increase in cardiovascular events seen.

**ADVERSE REACTIONS:** The most common adverse effects reported with celecoxib therapy include headache, diarrhea, rhinitis, nausea, dyspepsia, abdominal pain and sinusitis (see Table 4). Alterations in liver and biliary function were infrequent and returned to normal despite continued therapy. The adverse effects associated with rofecoxib should be similar to those reported with celecoxib.

Table 4: The Incidence of Celecoxib Adverse Effects from Four Studies:

Adverse Effect	Placebo (n=186)	Celecoxib 100 mg BID (n=107)	Celecoxib 200 mg BID (n=187)	Celecoxib 400 mg BID (n=87)
Headache	19.9%	3.7%	11.2%	11.5%
Diarrhea	2.7%	2.8%	6.4%	10.3%
Rhinitis	3.2%	0.9%	3.7%	8%
Nausea	3.8%	4.7%	3.2%	4.6%
Sinusitis	5.4%	0.9%	3.2%	4.6%
Dyspepsia	6.5%	4.7%	5.3%	2.3%
Abdominal pain	2.7%	2.8%	5.9%	2.3%

BID = twice daily administration

The incidence of adverse effects tended to be slightly higher in elderly patients but no substantial differences in safety and effectiveness were seen when comparing these patients and younger patients. The clinical trials included a large number of older patients including more than 2100 between 65 and 74 years of age and about 800 patients age 75 or greater.

These agents were designed to cause less gastrointestinal adverse effects. To determine the impact of celecoxib on the gastroduodenal mucosa and tissue, a number of endoscopy studies were conducted. These studies were designed to detect the development of erosions and ulceration. Endoscopic examinations were conducted by blinded evaluators at baseline and at other time points in the study.

One study evaluated the impact of celecoxib, naproxen and placebo on the gastroduodenal mucosa in 128 patients. The upper GI endoscopy was conducted at baseline and after 1 week of therapy. At baseline, the GI mucosa had to be normal; if there was evidence of inflammation, ulceration, erosion, petechiae or bleeding in the esophagus, stomach, pyloric channel or duodenum, the patient was excluded from the study. Also patients were excluded if they had a history of GI disease, medically significant chronic disease, current GI symptoms or had taken any NSAIDs, antiulcer medications, antacids, systemic glucocorticoids or antibiotics within 2 weeks of starting the study. Once the patient met the entry criteria they were started on celecoxib 100 or 200 mg, naproxen 500 mg or placebo twice daily for 7 days. The follow-up endoscopic examination was conducted between 2 and 4 hours after the morning dose of the study medication on day-7. After 1 week of therapy there were no gastric ulcers reported in the placebo or celecoxib groups, while the incidence in the naproxen group was 19%. The incidence of gastric erosions ranged from 9% to 13% with celecoxib or placebo and occurred in 72% of those treated with naproxen. While no cases of duodenal ulcers were observed in any of the patients, erosions were reported in 3% of the placebo group, 0% of the celecoxib 100 mg group, 6% of the celecoxib 200 mg group and 19% of the naproxen group.

According to the manufacturer only two patients ( 0.04%) out of 5285 patients who received celecoxib in the controlled clinical trials of 1 to 6 months duration at a daily dose of 200 mg or greater experienced significant upper GI bleeding. To date no controlled clinical trials have evaluated the risk of clinically significant bleeding with celecoxib vs. other NSAIDs. The risk of upper GI bleeding is also increased slightly in patients on celecoxib who take aspirin, about

11% of the patients on celecoxib in the clinical trials were also taking aspirin in doses of 325mg per day or less. While the endoscopic ulceration rate was increased in these patients, it was still less than the rate seen in patients in the comparator groups with or without aspirin.

Celecoxib in doses upto 600mg BID for 7 days or 800mg as a single dose had no effect on platelet aggregation or bleeding times.

Based on these results, celecoxib would be a safer agent for patients who are at increased risk of gastroduodenal ulceration (eg, elderly, high-dose therapy, history of GI problems, concomitant glucocorticoids, presence of cardiovascular disease or anticoagulant therapy).

**DRUG INTERACTIONS:** Celecoxib does not affect the pharmacokinetics of methotrexate or warfarin, nor does celecoxib affect the prothrombin time or INR in patients receiving warfarin therapy.

Based upon in-vitro data the package insert states that celecoxib is an inhibitor of CYP 450 2D6 which may lead to potential in-vivo interactions with agents that are metabolized by this enzyme. Limited data suggest that this inhibition is moderate and seen with much higher than prescribed doses of celecoxib. While the risk appears to be minimal there is no clinical data available to adequately evaluate the risk. The commonly used medications which are metabolized by this enzyme system include the following ( tri-cyclic antidepressants, codeine, tramadol, metoprolol, propranolol, timolol, haloperidol, respiridone, etc.) This is the same enzyme that is inhibited by paroxetine, fluoxetine, cimetidine, etc.

Lithium plasma levels increased by ~17% in healthy subjects who received celecoxib 200 mg BID suggesting that lithium levels may need to be followed whenever celecoxib is started or withdrawn.

The package insert also states the NSAID class labeling when it addresses the potential for celecoxib to diminish the antihypertensive effect of ACE inhibitors and the natriuretic effect of furosemide.

**DOSING:** The recommended therapeutic dose for the treatment of rheumatoid arthritis is celecoxib 100 mg to 200 mg twice daily. Osteoarthritis can be treated with celecoxib 200 mg once daily or 100 mg twice daily.

**COST:** Average wholesale price 100mg capsules \$1.43  
200mg capsules \$2.42

**PRODUCT AVAILABILITY:** Celecoxib was approved for the treatment of osteoarthritis and rheumatoid arthritis on December 31, 1998; approval is also being sought for the acute pain indication.

Rofecoxib – Vioxx by MSD will probably be available in 1999. The new drug application for this agent was filed with the FDA in November 1998.

**CONCLUSION:** Celecoxib, the first member of this new class of medications is safer than NSAIDs in terms of gastrointestinal toxicities and equally effective in the treatment of osteoarthritis and rheumatoid arthritis. At least one of these agents should be included in all formularies. While the exact place of these agents in therapy has not been established, it is logical that they will be the preferred agents for patients who are at risk of developing gastroduodenal ulcers, patients who need NSAIDs and are taking warfarin or who are at risk for bleeding. Whether they will be safer in patients at risk for renal effects from NSAIDs is not yet known. Celecoxib is also being studied in Alzheimers disease and in patients at risk for colonic polyps and carcinoma.

## NSAID Induced Gastropathy

The Arthritis Foundation conservatively estimates that at least 13 million patients in the U.S. with OA or RA regularly take NSAIDs. Table 3 applies the ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) data to their estimates.

**Table 3.** Estimated Annual Nonsteroidal Anti-inflammatory Drug (NSAID)-Associated Gastrointestinal (GI) Hospitalizations and Deaths in the United States

Diagnosis	NSAID Exposure (n)	Hospitalizations		Deaths	
		Incidence (%)	Patients (n)	Incidence (%)	Patients (n)
RA	2,000,000	1.5	30,000	0.22	4,400
Probable RA*	3,000,000	0.7 <sup>†</sup>	21,000	0.11 <sup>‡</sup>	3,300
OA	8,000,000	0.7	56,000	0.11 <sup>‡</sup>	8,800
Total	13,000,000		107,000		16,500

\* Estimated in the community, not under a rheumatologist's care.

<sup>†</sup> Estimated to be half; presumed milder disease as they are not under a rheumatologist's care.

<sup>‡</sup> Estimated from ratio of GI hospitalizations.

July 27, 1998 THE AMERICAN JOURNAL OF MEDICINE® Volume 105 (1B) 33S

the authors also estimate a conservative cost per hospitalization of \$10-15,000.00 or more than \$1 billion per year.

### ARAMIS data

- 92.5% of all hospitalizations for GI events in RA patients were related to NSAID use.
- annual hospitalization rate 1.46% for NSAID users vs 0.27% of non-NSAID users.
- overall about 10% of hospitalizations for upper GI bleeding result in death and 80% of all ulcer related deaths occurred in patients using NSAIDs.
- NSAID related ulcer deaths are about as common as death from asthma, malignant melanoma and cervical cancer combined.
- dyspepsia is a common side effect of NSAIDs but it does not correlate with endoscopic lesions or GI bleeds.
- 81% of RA patients in ARAMIS who had serious GI complications had no prior GI symptoms!
- about 80% of NSAID induced ulcers are gastric not duodenal.

### Risk Factors

- "chronologically gifted" (or 4% increase per year of age).
- duration of therapy
- higher doses of NSAID's
- combination of NSAID's
- use of prednisone
- history of NSAID induced gastropathy
- history of peptic ulcer disease
- history of GI bleeding
- cardiovascular disease
- warfarin
- taking antacids, sulcralfate, H2RA, PPI's
- H. pylori
- alendronate

**INDICATIONS:** Leflunomide is approved for the treatment of adults with active rheumatoid arthritis. The company will be able to promote the drug as an agent that is capable of reducing the signs and symptoms of rheumatoid arthritis and retard structural damage as evidenced by X-ray erosions and joint space narrowing.

**CLINICAL PHARMACOLOGY:** Leflunomide is an isoxazole immunomodulating agent with antiproliferative, anti-inflammatory and immunosuppressive activity. Leflunomide is classified as a pyrimidine synthesis inhibitor. It also exhibits weak analgesic and antipyretic activity.

Leflunomide also has an active metabolite, A77 1726 (M1). This metabolite is responsible for the majority of the pharmacologic activity of this compound. The metabolite interferes with lymphocyte activation, proliferation and differentiation. Antiproliferative effects appear to be mediated by inhibition of *de novo* pyrimidine biosynthesis, specifically dihydro-orotate dehydrogenase.

A77 1726 also inhibits receptor-associated tyrosine kinase activity that is responsible for signal transduction. The effects on both pyrimidine biosynthesis and tyrosine kinase activity play a role in the drug's antiproliferative and immunosuppressive activity. Other postulated mechanisms include promotion of TGF- $\beta$ 1 production, inhibition of IL-2 production and modulating homotypic adhesion of peripheral blood and synovial fluid mononuclear cells.

Leflunomide has synergistic activity with cyclosporine, rapamycin and brequinar, while additive or antagonistic activity may occur with mycophenolate, depending on conditions.

Leflunomide inhibits T-lymphocyte and B-lymphocyte activation and proliferation. It also impairs the activity of cytokines; inhibits the action of IL-3, IL-4, G-CSF, GM-CSF and TNF- $\alpha$ ; and inhibits IgM and IgG production. In transplant models, proliferation of vascular smooth muscle cells is prevented (mesenchymal cells) in donor organs, and the levels of autoantibodies, alloantibodies and xenoantibodies are reduced. In patients with rheumatoid arthritis, immunomodulatory effects include inhibition of mononuclear cell adhesion and aggregation. Although immunosuppressive, when administered in animal septicemia models it did not alter the resistance to bacterial pathogens.

Animal models for autoimmune disorders including experimental allergic encephalomyelitis against myelin-basic protein as a model of multiple sclerosis, myasthenia gravis, glomerulonephritis, tubulointerstitial nephritis, uveitis, adjuvant arthritis, proteoglycan-induced arthritis and systemic lupus erythematosus have beneficial activity with leflunomide. It is also active in the prevention of rejection of skin, vascular, cardiac, islet, intestine, lung and kidney transplants, treatment of ongoing acute rejection, prevention and treatment of chronic allograft rejection and suppression of graft versus host disease.

**PHARMACOKINETICS:** Leflunomide is converted to the active metabolite A77 1726. Peak levels of A77 1726 occur within 6 to 12 hours following oral administration. Administration with food or high-fat meals does not impact A77 1726 plasma levels. Plasma protein binding is extensive (>99%) and volume of distribution is 0.13 L/kg (*V<sub>ss</sub>*). The elimination of A77 1726 is linear for 5 to 25 mg doses of leflunomide. The mean plasma half-life is 15 to 18 days. Elimination is via biliary and urinary excretion.

Clearance appears unaffected by age. Smoking can increase the clearance of A77 1726 by 38%, but no difference in clinical efficacy has been seen between smokers and nonsmokers. Peritoneal dialysis and hemodialysis have little effect on A77 1726 plasma levels or clearance. But, leflunomide should be used with caution in patients with chronic renal failure since the free fraction of A77 1726 can be doubled. Leflunomide therapy should be avoided in patients with hepatic insufficiency until more information is available regarding the safety and elimination of this product in this patient population.

**COMPARATIVE EFFICACY:** The effects of leflunomide were evaluated in a placebo controlled, double-blind study enrolling 402 patients with active rheumatoid arthritis. Patients were treated with leflunomide 5 mg, 10 mg or 25 mg or placebo daily for 6 months following a 3-month washout period after discontinuation of prior gold, methotrexate or azathioprine therapy. Stable doses of NSAIDs and corticosteroids at doses of 10 mg or less of prednisone (or equivalent) daily were permitted. Leflunomide therapy was initiated with a single oral loading dose of 50 mg in the 5 mg group and 100 mg in the 10 mg and 25 mg groups. Results of this study are summarized in Table 1. Although a high rate of placebo response was observed, both the 10 mg and 25 mg leflunomide doses were shown to be more effective than placebo.

Table 1: Efficacy of Leflunomide:

Outcome Measure **	Placebo (n=102)	5 mg/d (n=95)	10 mg/d (n=100)	25 mg/d (n=101)
Swollen joint score	-12.8	-16.9	-20.2*	-20.4*
Tender joint score	-23.6	-25.1	-31	-35.3*
Swollen joint count	-6.5	-7.6	-10.4*	-11.7*
Tender joint count	-9.7	-10.5	-13.6	-16.5*
Patient global assessment	0.5	0.6	1.1*	1*
Physician global assessment	0.6	0.7	1.1*	1.1*
Health Assessment Questionnaire score	-8.1	-5.8	-14.5*	-13.6*
Pain assessment, VAS	0.3	0.3	-0.91*	-1*
Grip strength, mmHg	14.5	4.6	30.8*	52.4*
Morning stiffness, minutes	-33.7	-48.3	-55.3	-71.8*
Erythrocyte sedimentation rate, mm/hr	3.1	4.2	-5.2*	-5.4*
C-reactive protein normalized, number of patients	14	9	26*	32*

\* p<0.05 versus placebo

\*\* negative values for joint counts, scores, morning stiffness and ESR indicate improvement; positive values for global assessments and grip strength indicate improvement

An open-label extension study enrolling 300 patients from this study and 50 patients from a leflunomide pharmacokinetic study was conducted to determine the long-term effectiveness of leflunomide therapy. Continued activity was demonstrated with long-term therapy, and 204 of the 350 patients were able to take the leflunomide for 18 months.

The patients enrolled in the previously discussed studies are most likely included in the results discussed in the product labeling. But, the number of patients enrolled in the studies reported in the product labeling are higher than these previously published results.

The key efficacy parameter used in the clinical studies reported in the product labeling was the ACR20 Responder Index. This index combines clinical, laboratory and functional measures. A patient was classified as a ACR20 responder if they had a 20% or better improvement in both the number of tender and swollen joints and improvement in three of the following five criteria: physician global assessment, patient global assessment, function/disability measure (Modified Health Assessment Questionnaire), visual analog pain scale and erythrocyte sedimentation rate or C-reactive protein. Changes in structural damage were done using the Sharp Score which is a composite score of erosions and joint space

narrowing in the hands, wrists and forefeet.

The labeling contains the results of three clinical trials (US301, MN301 and MN302). All the patients in these studies had active rheumatoid arthritis. They were given an initial oral loading dose of leflunomide of 100 mg/day for 3 days. Then the dose of leflunomide was reduced to 20 mg/day.

Study US301 was a randomized placebo controlled evaluation of 482 patients with active rheumatoid arthritis. The duration of disease had to be at least 6 months prior to the start of the study medication. Patients were randomly assigned to treatment with leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week which could be increased to 15 mg/week (n=182) or placebo (n=118) for 52 weeks. In addition, all patients were given folate 1 mg twice daily. More patients receiving leflunomide were classified as ACR Responders within 1 month than those in the methotrexate and placebo group. By the end of 3 months the number of patients classified as ACR Responders was similar in both the leflunomide and methotrexate groups. At the end of the year of treatment ~41% of the leflunomide, ~35% of the methotrexate and ~18% of the placebo groups were classified as ACR20 Responders. Both the leflunomide and methotrexate were better than placebo, but the difference between the leflunomide and methotrexate was not significant.

Study MN301 was a randomized placebo controlled evaluation of 358 patients with active rheumatoid arthritis. Patients were randomly assigned to treatment with leflunomide 20 mg/day (n=133), sulfasalazine 2 g/day (n=133) or placebo (n=92) for 24 weeks. After the initial 24 weeks, patients were invited to continue in an optional 6-month blinded comparison of the leflunomide and sulfasalazine. At the end of the first 24 weeks of treatment, ~58% of the leflunomide, ~44% of the sulfasalazine and ~28% of the placebo groups were classified as ACR20 Responders. Both the leflunomide and sulfasalazine were better than placebo but the difference between the leflunomide and sulfasalazine was not significant.

Study MN302 was a randomized comparison of leflunomide and methotrexate in the treatment of active rheumatoid arthritis. Patients were assigned to treatment with leflunomide 20 mg/day (n=501) or methotrexate 7.5 mg/week (which could be increased to 15 mg/week) for 52 weeks. Folate supplementation was not given to all patients; instead only 10 of the patients were given folate supplementation. At the end of the year of treatment, ~43% of the leflunomide and ~66% of the methotrexate groups were classified as ACR20 Responders (p<0.0001).

In these three studies, leflunomide, methotrexate and sulfasalazine were able to reduce disease progression as measured by the Sharp Score. Patients treated with placebo experienced a worsening in their Sharp Score.

Results of studies comparing leflunomide with cyclosporine, gold and methotrexate were published in abstract form. In these studies, leflunomide's effectiveness was most similar to methotrexate.

Studies of leflunomide in patients with psoriasis and systemic lupus erythematosus are underway. Although in animal models leflunomide showed promise in the prevention of organ rejection, its long half-life would limit the ability to make frequent dose adjustments. Development has therefore been limited to use in autoimmune diseases. Analogs of A77 1726 are being evaluated for potential use in the prevention and treatment of graft rejection

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Leflunomide is contraindicated in patients with known hypersensitivity reactions to leflunomide and any of the product ingredients (colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc and titanium dioxide). Also yellow ferric oxide can be found in the 20 mg tablet.

Leflunomide should not be used in pregnant women, in patients with significant liver disease or positive hepatitis B or C serologies. Leflunomide has been classified as Pregnancy Category X. Therefore, pregnancy must be ruled out prior to the start of leflunomide therapy. Female patients should also be

advised to avoid getting pregnant during leflunomide therapy and prior to the completion of the drug elimination from the body. The product should also be avoided in female patients who are not using reliable contraception or birth control methods. If the female patient wishes to become pregnant, leflunomide therapy should be discontinued and cholestyramine 8 grams three times daily for 11 days should be given. After the cholestyramine therapy, blood samples need to be drawn to detect A77 1726, the active metabolite of leflunomide. Conception should not begin until the plasma levels for A77 1726 are less than 0.02 mg/L on two separate tests at least 14 days apart. It may take up to 2 years to reach undetectable plasma concentrations of A77 1726 even with the use of cholestyramine therapy.

The manufacturer does not recommend the use of leflunomide by nursing mothers. It is unknown if leflunomide is excreted in human milk.

Leflunomide can cause elevations in liver enzymes. Most elevations were classified as mild ( $\leq$  2-fold upper limits of normal) and usually improved while continuing therapy. Fewer patients experienced a greater than three-fold increase above the upper limits of normal; this increase reversed after the dose was decreased or the drug was discontinued.

The safety and effectiveness of leflunomide therapy in patients with severe immunodeficiency are unknown. Therefore, leflunomide is not recommended in patients with severe immunodeficiency, bone marrow dysplasia or severe, uncontrolled infection. Nor should patients receiving leflunomide be given a live vaccine.

**ADVERSE REACTIONS:** The most common side effects of leflunomide reported in the published clinical studies have include diarrhea, rash, alopecia and elevated liver function tests. Other side effects include pruritus, anorexia, abdominal pain, nausea, vomiting, gastritis, gastroenteritis, hypertension, dizziness and transient thrombocytopenia. Side effects were most common with the 25 mg dose.

The most frequent side effects listed in the product labeling are diarrhea, elevated liver enzymes, alopecia and rash. Other side effects that have been reported include allergic reactions, asthenia, flu syndrome, infection, injury accident, pain, abdominal pain, back pain, hypertension, chest pain, anorexia, dyspepsia, gastroenteritis, nausea, abdominal pain, mouth ulcer, vomiting, hypokalemia, weight loss, arthralgia, leg cramps, joint disorder, synovitis, tenosynovitis, dizziness, headache, paresthesia, bronchitis, increased cough, respiratory infection, pharyngitis, pneumonia, rhinitis, sinusitis, eczema, pruritus, dry skin and urinary tract infection.

**MONITORING:** Liver function tests need to be obtained at baseline and at monthly intervals. If the liver function tests are stable, less frequent monitoring can be done based on the individuals' clinical situation.

Uric acid levels may change during leflunomide therapy. Leflunomide has a uricosuric effect on the brush border of the renal proximal tubule. This has not been shown to be a problem during leflunomide therapy, but may explain why the uric acid level may change in a patient receiving leflunomide therapy.

**DRUG INTERACTIONS:** Administration with cholestyramine or activated charcoal reduced levels of the active metabolite by 40% to 50% within 24 hours. The reduction in levels is probably the result of preventing biliary recycling of A77 1726.

A77 1726 is an inhibitor of CYP 450 2C9. This isoenzyme is responsible for the metabolism of some nonsteroidal anti-inflammatory agents. The importance of this *in vitro* finding has not been determined, so caution is recommended for patients requiring NSAID therapy in addition to the leflunomide. Caution is also recommended for patients who are also receiving rifampin therapy. Rifampin can increase the peak plasma levels of A77 1726 by 40%. Caution is probably also warranted with other rifamycins (eg, rifabutin and rifapentine) and enzyme inducers.

Use of leflunomide with methotrexate and other known hepatotoxic agents may increase the risk of hepatotoxicity.

Patients receiving tolbutamide should have their blood glucose closely monitored after starting

leflunomide therapy. A77 1726 can increase the free fraction of tolbutamide by 13% to 50%, based on *in vitro* studies. The resultant increase in free fraction may improve the patients' blood glucose levels, but may also increase the risk of hypoglycemia.

**DOSING:** Leflunomide 10 mg and 25 mg once daily is effective in the treatment of active rheumatoid arthritis. Additional studies evaluating 10 mg and 20 mg dosages have also been performed, although results of these studies have not yet been published.

The manufacturers recommend an initial oral loading dose of 100 mg for 3 days. The dose is then decreased to 20 mg/day. Doses higher than 20 mg/day are not recommended. No adjustments in dose are necessary for patients over 65 years of age. Lower doses may be recommended for patients with altered liver function tests (see Table 2) or patients who are unable to tolerate the 20 mg/day dose.

Leflunomide is not indicated for use in children less than 18 years of age since the safety and efficacy of leflunomide in this patient population has not been established.

Table 2: Recommended Dosage Adjustments in Leflunomide Therapy Based on Liver Function:

Liver Function Test	Action	Recommended Dose
ALT elevation >2-fold ULN	Decreased dose	10 mg/day
ALT >2 but $\leq$ 3-fold ULN despite dose reduction	Liver biopsy B if continued treatment is desired	10 mg/day
ALT >3-fold ULN despite cholestyramine therapy and dose reduction	Discontinue the leflunomide and give cholestyramine	

ULN = upper limit of normal

Leflunomide can be used in combination with aspirin, nonsteroidal antiinflammatory agents and/or low-dose corticosteroids. The safety of using leflunomide in combination with antimalarials, intramuscular or oral gold, D-penicillamine, azathioprine or methotrexate has not been established.

**PRODUCT AVAILABILITY:** In August 1998, the FDA Arthritis Advisory Committee recommended the approval of leflunomide. Leflunomide was approved for marketing in the United States in September 1998. The product is marketed by Hoechst Marion Roussel and is available as a 10, 20 and 100 mg tablet. The 100 mg tablet is only intended for use as a 3-day starting dose and should not be used for chronic therapy.

Arava 100mg - \$40.80 per dose AWP  
 20mg - \$8.16 per dose AWP  
 10mg - \$8.16 per dose AWP

The tablets should be stored at controlled room temperature of 25°C and protected from light. The temperature can be allowed to range from 15 to 30 degrees C.

**CONCLUSION:** Leflunomide appears to be an effective agent for use as DMARD therapy in patients with rheumatoid arthritis. Leflunomide is as effective as methotrexate and sulfasalazine in the treatment of active rheumatoid arthritis. So this drug will be an effective alternative to methotrexate and sulfasalazine in patients that are not good candidates for these drugs or unable to tolerate these agents. Whether, leflunomide should be used prior to trying methotrexate or sulfasalazine remains to be determined.