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Valdecoxib: A new cox-2-specific inhibitor

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Introduction

Valdecoxib (Bextra®) is the newest addition to the cyclooxygenase-2 (COX-2) inhibitor family that already includes celecoxib (Celebrex®) and rofecoxib (Vioxx®). It was approved by the FDA on November 21, 2001 and is marketed by Pharmacia and Pfizer, the same makers of celecoxib. Valdecoxib is an oral agent and is currently indicated for the relief of the signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA) and for the treatment of primary dysmenorrhea.[1] It also appears to be effective in the treatment of acute pain, although it is not yet FDA approved for this indication. In addition, a parenteral form of valdecoxib, that will be available as the prodrug parecoxib, is currently undergoing phase III clinical trials for the management of acute post-surgical pain.[2,3]

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat arthritis, menstrual pain, headaches, and other painful conditions due to their ability to relieve the inflammation process and provide general analgesia. However, their long-term use is limited by side effects including damage to the gastric mucosa and renal toxicity. The most common adverse effect associated with NSAID use is gastrointestinal (GI) toxicity, often resulting in ulcers, bleeding, or perforations. Currently, none of the available NSAIDs is free of GI complications.

The clinical effects of traditional NSAIDs are based on inhibiting the COX enzyme, which is responsible for the conversion of arachidonic acid to prostaglandin (PG).[4] Two COX isoforms have been identified: COX-1 and COX-2. COX-1 is constitutively expressed and is present as the main COX enzyme in the gastric mucosa, where it is the primary source of PGs. Prostaglandins are involved with cytoprotection of gastric mucosa, hemostasis, and renal physiology, as well as being produced in response to inflammation and pain. In contrast, COX-2 is inducibly expressed during the inflammation process. It is believed that inhibition of COX-2 is the basis for the anti-inflammatory, antipyretic, and analgesic effects of these agents, while inhibition of COX-1 is the cause of adverse GI effects.

The development of the COX-2 selective inhibitors, while minimally inhibiting COX-1, has proved to be very effective in providing relief of pain and inflammation with improved GI tolerability. As an example, since its introduction in 1999, COX-2 inhibitors now account for about 60% of the antiarthritic drug market.[5] Total sales of Celebrex® and Vioxx® in the year 2000 were estimated to be more than $3 billion, with new and refill prescriptions rising to 121.3 million. This article will review the pharmacology, pharmacokinetics, clinical trials, adverse effects, contraindications, drug interactions, dosing, and cost of therapy with valdecoxib.

Pharmacology/Pharmacokinetics

The COX enzyme plays a key role in the biosynthesis pathway of PGs. The inhibition of COX-2 by valdecoxib is believed to result from a three-step kinetic mechanism.[6] The first two steps

Table 1: Pharmacokinetic parameters of Valdecoxib[1]

C_{max}	161 mg/L
T_{max}	~3 hours
Oral bioavailability	83%
AUC	1479 mg·hr/L
Effect of food	T_{max} delayed 1-2 hrs, but no significant effect on AUC or C_{max}.
Effect of antacid (Al/Mg OH)	No effect on AUC.
Plasma protein binding	98%
Volume of distribution	86 L
Metabolism	Mainly CYP450 3A4 and 2C9. Also, non-P450 dependent pathways (i.e. glucuronidation).
Excretion	70% excreted in urine as metabolites, 20% as glucuronide.
Oral clearance	6 L/hr
$T_{1/2}$	8-11 hours

C_{max} = Maximum plasma concentration; T_{max} = Time to C_{max} ; AUC = Area under curve; $T_{1/2}$ = Half-life

are reversible equilibrium processes, leading to an irreversible reaction between enzyme and inhibitor. It is this third step that is postulated to contribute to the selectivity for COX-2. The first step may involve an interaction between the inhibitor and a hydrophobic pocket on the COX enzyme surface leading to the active COX site. The second step is hypothesized to involve some conformational changes so that the inhibitor moves to the active site. The final step involves the inhibitor binding to the enzyme to form an irreversible complex. Binding of valdecoxib to the COX-2 enzyme now prevents formation of PGs, leading to a decrease in pain and inflammation.

Some of the pharmacokinetic characteristics of valdecoxib are presented in Table 1. These values are based on steady state plasma concentrations in healthy male subjects (n=8, ages 20-42 years).[1]

Clinical Trials

Approval of valdecoxib by the FDA was given based on the results of 5 randomized, placebo-controlled trials in 3,918 patients with OA of the knee or hip treated for 3 to 6 months; on 4 randomized, placebo-controlled trials in 3,444 patients with RA treated for 3 to 6 months; and on 2 placebo-controlled studies of women (number unspecified) with moderate to severe primary dysmenorrhea.[1,7] These studies demonstrated that valdecoxib was significantly superior over placebo and exhibited comparable efficacy to the NSAID naproxen for all three indications. The results of these trials have not been published to date, but several of them have been presented as abstracts at clinical meetings. The available studies are discussed below and summarized in table 2.

Table 3. ACR 20 Response Rate (%) in RA[1]

Drug/Dose	Study 1	Study 2
Valdecoxib 10 mg/day	49% (103/209)	46% (103/226)
Valdecoxib 20 mg/day	48% (102/212)	47% (103/219)
Naproxen 500 mg bid	44% (100/225)	53% (115/219)
Placebo	32% (70/222)	32% (71/220)

Osteoarthritis

The 3 randomized, placebo-controlled, double-blinded, multi-center trials assessed the efficacy of valdecoxib for the treatment of the signs and symptoms of osteoarthritis of the knee or hip. All of these studies looked at improvement in three areas of OA symptoms: overall patient assessment of pain using the visual analog scale, the patient's global assessment, and the WOMAC (Western Ontario and McMaster Universities) OA index, a composite of pain, stiffness, and functional measures in osteoarthritis. Fiechtner *et al.* studied valdecoxib in doses of up to 10 mg bid compared to naproxen 500 mg bid and placebo in 642 patients with OA of the knee.[8] This six-week study found valdecoxib (5 mg, 10 mg qd, and 10 mg bid) to be comparable in efficacy to naproxen and demonstrated a dose-dependent improvement, with no additional benefit conferred with doses above 5 mg bid or 10 qd. Kivitz *et al.* evaluated 1,019 patients with osteoarthritis of the knee for 12 weeks and found greater improvement of arthritic symptoms with valdecoxib in doses of up to 20 mg when compared with naproxen 500 mg bid.[9] Also, this study investigated the incidence of gastroduodenal ulcers by pre- and post-therapy endoscopies. However, the criteria for ulcer definition were not specified. The higher incidence of ulcers seen in the naproxen group were statistically significant only at valdecoxib doses of 5 and/or 10 mg. Makarowski *et al.* studied 466 patients with osteoarthritis of the hip for 12 weeks and found a greater improvement in the overall assessment of arthritic relief with valde-

Table 2. Summary of Valdecoxib Clinical Studies[7]

Authors	Study Design/ Patients	Treatment Groups	Clinical Findings
Fiechtner *et al.* 2001[8]	OA R, DB, PC, PG, MC N = 642	Val 0.5, 1.25, 2.5, 5, 10 mg bid, 10 mg qd; Nap 500 mg bid; P	All Val doses except 0.5 mg showed greater improvement over placebo. Val 5 mg bid, 10 mg qd, and 10 mg bid have similar efficacy to Nap.
Kivitz *et al.* 2001[9]	OA R, DB, PC, MC N = 1,019	Val 5, 10, or 20 mg qd; Nap 500 mg bid; P	Comparable improvement with Val 10 mg and 20 mg and Nap. Higher ulcer incidence with Nap (10%) vs. Val 5 mg (3%), Val 10 mg (3%), and Val 20 mg (5%).
Makarowski *et al.* 2001[10]	OA R, DB, PC, MC; N = 466	Val 5 or 10 mg qd; Nap 500 mg bid; P	Greater improvement with Val 5 and 10 mg over placebo. Similar efficacy with Val 10 mg and Nap.
Bensen *et al.* 2001[11]	RA R, DB, PC; N = 1,089	Val 10, 20, or 40 mg; Nap 500 mg bid; P	Greater ACR-20 rates with all Val doses (46-52%) and Nap (44%-51%) than with placebo (30-36%).
Torri *et al.* 2001[12]	PD R, DB, PC N = 120	Single doses of Val 20 mg and 40 mg; Nap 550 mg; P	Greater pain intensity relief with Val 40 mg at all time points. Greater pain reduction on time-weighted scales with both Val doses and Nap over placebo.
Camu *et al.* 2002[13]	AP R, DB, PC, MC N = 217	Val 20 or 40 mg bid; P	34.5% and 38.9% reduction of mean morphine consumption with Val 20 and 40 mg, respectively, 0-24 hours postop.
Daniels *et al.* 2001[14]	AP R, DB, PC N = 466	Val 10, 20 40, or 80 mg; P	Longer median time to rescue med postop with all Val doses (9:04 to >24:00) vs. placebo (2:59). Less % of pts requiring rescue med postop with all Val doses (32-67%) vs. placebo (95%).
Fricke *et al.* 2002[15]	AP R, DB, PC N = 203	Val 40 mg; Rof 50 mg	Quicker onset of analgesia, improved pain relief, and lower pain intensity with Val vs. Rof after single dose; Superior efficacy with Val in % of pts requiring rescue med.

OA = Osteoarthritis; RA= Rheumatoid arthritis; PD – Primary dysmenorrhea; AP = Acute Pain; R = Randomized; DB = Double-blind; PC = Placebo-controlled; PG = Parallel-group; MC = Multicenter; Val = Valdecoxib; Nap = Naproxen; P = Placebo

coxib 5 and 10 mg compared to placebo. In addition, the authors found the 10 mg dose to be equally efficacious as naproxen 500 mg bid.[10]

Rheumatoid arthritis

Two important three month trials compared valdecoxib to naproxen and placebo in the reduction of the signs and symptoms of RA, as measured by the ACR (American College of Rheumatology) 20 index. This index is a composite defined as a 20% improvement in the number of tender and swollen joints, as well as, a 20% improvement in three of five other measures (patient global, physician global, patient pain, patient function assessment, and the erythrocyte sedimentation rate).[1] These results are briefly shown in table 3.

Only one study, discusses the clinical efficacy of valdecoxib in the treatment of the signs and symptoms of rheumatoid arthritis. Bensen *et al.* evaluated valdecoxib in doses up to 40 mg qd in 1,089 patients compared to naproxen and placebo.[11] A significant improvement in response was seen with greater ACR 20 rates in all three valdecoxib doses compared to placebo, but there was no change compared to the naproxen groups. Interestingly, the 20 mg dose demonstrated to be as efficacious as the 40 mg dose and appeared to be better tolerated.

Primary dysmenorrhea

Torri *et al*. compared two different doses of valdecoxib to naproxen and placebo over four months in 120 women with moderate to severe primary dysmenorrhea.[12] All active treatments resulted in significant pain relief and reduction in pain intensity over 8 and 12 hours. Valdecoxib was comparable to naproxen, with valdecoxib 40 mg being significantly better than 20 mg on the 12-hour pain intensity measurement. Also, valdecoxib 40 mg provided 5 more hours of pain relief than the 20 mg dose.

Acute pain

Valdecoxib has been studied in the setting of postoperative analgesia, although it does not have FDA approval for this indication to date. The

Table 4. Adverse events (%) with >2% incidence in OA or RA patients treated with valdecoxib for >3 months[1]

Adverse event	Placebo (n = 973)	Valdecoxib 10 mg (n = 1214)	Valdecoxib 20 mg (n = 1358)
Hypertension	0.6	1.6	2.1
Back pain	1.6	1.6	2.7
Peripheral edema	0.7	2.4	3.0
Flu-like symptoms	2.2	2.0	2.2
Accidental injury	2.8	4.0	3.7
Dizziness	2.1	2.6	2.7
Headache	7.1	4.8	8.5
Abdominal fullness	2.0	2.1	1.9
Abdominal pain	6.3	7.0	8.2
Diarrhea	4.2	5.4	6.0
Dyspepsia	6.3	7.9	8.7
Flatulence	4.1	2.9	3.5
Nausea	5.9	7.0	6.3
Myalgia	1.6	2.0	1.9
Sinusitis	2.2	2.6	1.8
Upper respiratory tract infection	6.0	6.7	5.7
Rash	1.0	1.4	2.1

study by Camu *et al*. in 2002 was a multicenter, double-blind, parallel-group involving 217 patients and investigated the opioid-sparing effects, analgesic efficacy, and safety of valdecoxib.[13] Patients undergoing hip arthroplasty were given active drug or placebo 1 to 3 hours preoperatively and were followed postoperatively for 48 hours. Patients who received valdecoxib 20 mg or 40 mg bid required significantly less morphine than placebo. Administration of valdecoxib before and after surgery reduced the amount of morphine needed for pain relief and provided greater analgesic efficacy when compared to morphine alone. There was no significant difference between the percentages of patients requiring morphine at scheduled time points above 48 hours in the valdecoxib versus the placebo groups.

Two recent studies evaluated the efficacy of valdecoxib in relieving postoperative pain associated with oral surgery. One study presented in abstract form by Daniels *et al.* was a randomized, double-blinded, placebo-controlled single-dose study of 466 patients with valdecoxib.[14] The results suggest that valdecoxib is effective in increasing the median time to rescue medication, as well as, in decreasing the number of patients requiring rescue medication after surgery compared to placebo. Finally, a recent randomized, double-blinded study published by Fricke *et al.* evaluated the analgesic efficacy of valdecoxib 40 mg compared to rofecoxib 50 mg and placebo.[15] Results showed that valdecoxib was superior to placebo in all areas of improvement, including onset of analgesia, pain relief, pain intensity, and patient satisfaction.

Adverse Effects

Table 4 summarizes the adverse events occurring in >2% of patients treated with valdecoxib 10 mg or 20 mg/day. This data comes from 7 controlled clinical trials with a duration of 3 or more months.[1] Of these patients, 2665 had OA and 2684 had RA. In addition, over 4000 of them received a chronic total daily dose =10 mg/day and about 2800 received this dose for at least 6 months, while 988 received it for over a year.

Contraindications and Warnings

Valdecoxib is contraindicated in patients with known hypersensitivity to any of the COX-2 inhibitors.[1] Valdecoxib should not be given to patients with asthma, urticaria, or allergic-type reactions to aspirin or non-steroidal anti-inflammatory drugs due to the risk of anaphylaxis.[16] This includes patients with the aspirin triad (asthma with rhinitis with or without nasal polyps or bronchospasm). Also, valdecoxib should be used with caution in patients on concurrent corticosteroid therapy. Patients with a history of GI bleeding or ulcers

Table 5. Drug-Drug Interactions with Valdecoxib[1,7,16,17]

Aspirin	Does not affect cardioprotective effect but increases risk of GI complications.
Warfarin	Increase in plasma exposure of warfarin and risk of increased anticoagulation.
Methotrexate	No effect on plasma exposure or renal clearance of methotrexate.
ACE-Inhibitors	May decrease antihypertensive effects.
Furosemide	Decreased response to furosemide due to inhibition of renal prostaglandin synthesis.
Dextromethorphan	Increased levels of dextromethorphan due to CYP 2D6 and 3A4 inhibition.
Lithium	Decreased clearance and increased serum levels of lithium (monitor).
Fluconazole and ketoconazole	Increased blood levels of valdecoxib due to 3A4 and 2C9 inhibition
Glyburide	No effect.

should be aware that serious GI toxicity such as bleeding, ulceration, or perforation of the stomach, small intestine, or large intestine can occur at any time when treated with NSAIDs.[1] Patients with advanced renal or hepatic disease are not advised to take valdecoxib because of a lack of safety data.[1,16]

Patients with fluid retention, hypertension, or heart failure are advised to use valdecoxib with caution.[16,17] It should not be administered to patients with preexisting asthma since there is a possibility that aspirin-sensitive asthma can cross-react with NSAIDs to cause severe bronchospasms.[1] Patients with mild or moderate hepatic impairment are cautioned about the use of valdecoxib since elevations of aminotransferases (AST and AST) may occur; therefore, they should be monitored for signs and symptoms of liver dysfunction.[1] Long-term use of NSAIDs has been associated with renal injury so patients with mild or moderate renal impairment should be monitored carefully when treated with valdecoxib.[1] In particular, caution should be taken in patients with serious dehydration; it is advisable to rehydrate before beginning treatment.[1,16] Also, valdecoxib is classified as a pregnancy Category C drug and should be avoided in late pregnancy due to the risk of premature closure of the ductus arteriosus and other teratogenic effects.[17] In the pediatric population (<18 yo), safety and effectiveness of valdecoxib has not been studied so precaution is advised.[1,16,17]

Drug Interactions

In general, metabolism of valdecoxib occurs via CYP 3A4 and 2C9 with glucuronidation being a minor (20%) route of metabolism.[1,7] In vitro studies show valdecoxib to be a moderate inhibitor of CYP 2C19 and a weak inhibitor of both 3A4 and 2C9.[1] Studies investigating potential drug interactions were done with valdecoxib and its prodrug, parecoxib.[1] Some of the known drug interactions of valdecoxib are reported in Table 5.

Dosing and Administration

The recommended oral dose of valdecoxib is the same for OA and RA: 10 mg once a day. The recommended dose for primary dysmenorrhea is 20 mg twice daily. A dose of 20 mg twice a day has also been used in the treatment of acute pain; however, this indication is not FDA-approved. As mentioned earlier, valdecoxib will soon be available in an IV or IM form for use with postoperative pain. Recent clinical trials have used doses ranging from 20 to 80 mg, with the 20 mg and 40 mg often showing analgesic efficacy.[3]

In certain special populations, doses of valdecoxib may need to be adjusted. For mild to moderate hepatic impairment, doses of valdecoxib should not exceed 10 mg, and signs of edema should be monitored. However, no dosage adjustment is needed for mild to moderate renal impairment. In the geriatric population, no special dosage adjustment is needed unless they have poor general health or other precautions that may warrant a decrease in dose. As discussed earlier, caution is advised for use in children under 18 years of age because safety and efficacy has not been evaluated in this population yet.

Cost

The average cost of a 30-day supply of Bextra® from three local community pharmacies is $84.01, ranging from $80.33 to $87.99. The price is the same for the 10 mg or 20 mg tablets.

Summary

Valdecoxib is the newest FDA-approved COX-2 inhibitor for the treatment of OA, RA, and primary dysmenorrhea. Future indications include its use in the postoperative analgesic setting, particularly with the availability of the parenteral dos-

age form. Valdecoxib appears to be similar in profile to the other COX-2 inhibitors and comparable in efficacy to other NSAIDs like naproxen.

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Strattera® (atomoxetine) is a selective norepinephrine reuptake inhibitor used in the treatment of attention-deficit/hyperactivity disorder (ADHD). It has a different mechanism of action from the stimulant-like drugs that have been used to treat ADHD in the past. It is thought to selectively inhibit the pre-synaptic norepinephrine transporter and does not appear to have a potential for abuse so it is not classified as a controlled substance. The initial dose for children =6yrs/=70kg is 0.5 mg/kg/day given qam or in 2 divided doses. The dose may be increased after 3 days to a target of 1.2 mg/kg/day. The initial dose for adults and children =6yrs/=70kg is 40 mg/day given qam or in 2 divided doses. The dose may be increased every 3 days to a target of 80 mg/day. Adjustment is necessary in patients with hepatic impairment and those on CYP 2D6

LEXAPRO™
A new Selective serotonin reuptake inhibitor

Surjit Singh, Pharm.D. Candidate

Introduction

Depression is a major public health problem in the United States. The National Comorbidity Survey reports that 17% of the United States population has had or will have a major depressive disorder in their lifetime and more than 10% has had an episode of depression within the last year.[1] Depression is more prevalent in females than males and adults 25 to 44 years of age experience the highest rates of depression.[1] Also, even though depression may occur regardless of age or gender, rates of alcoholism, substance abuse, suicide attempts, and deaths are higher in these young patients. In addition, patients with depression are more likely to develop co-morbid psychiatric disorders. Currently, there are six Selective Serotonin Reuptake Inhibitors (SSRIs) that are approved for the treatment of depression. Lexapro™ (escitalopram), is the latest in this class. It was approved in August 2002 by the Food and Drug Administration (FDA) and is being marketed by Forest Pharmaceuticals, Inc.

Escitalopram is the S-enantiomer of citalopram. Animal studies demonstrate that the biological effects of citalopram reside within the S-enantiomer.[2] However, clinical trials have been unable to demonstrate escitalopram's superiority over citalopram and there is no evidence that escitalopram has a lower frequency of side effects than the parent compound. Nevertheless, it may have the potential advantage of a quicker onset of action.[3]

Pharmacodynamics

Escitalopram enhances the effects of serotonergic activity in the central nervous system (CNS) by inhibiting the neuronal reuptake of serotonin. Like other SSRIs, escitalopram is highly selective for serotonin and has minimal effects on other neurotransmitters. Therefore, it causes less sedation, anticholinergic and cardiovascular effects than the tricyclic antidepressants.

Pharmacokinetics

Pharmacokinetic parameters of escitalopram are similar to citalopram. A 20 mg dose of escitalopram is bioequivalent to 40 mg of citalopram. Escitalopram is extensively metabolized by CYP450 isozymes 2C19, 2D6, and 3A4. Therefore, theoretically, impaired activity of any one of these isozymes should have a minimal effect on the net metabolic clearance.[4] Escitalopram is metabolized to two inactive metabolites: S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). Escitalopram is recovered in the urine as citalopram (8%) and S-DCT (10%). Absorption of escitalopram is not affected by food; whereas, it's area under the curve (AUC) and half-life are increased by approximately 50% in elderly patients. The elimination half-life of escitalopram is approximately 25 hours which makes it ideal for once daily dosing.

Indication and Dosing

Escitalopram is approved for the treatment of major depressive disorder; however, initial studies have shown that within 1-2 weeks escitalopram also demonstrates significant antianxiety and antidepressant effects. The initial adult dose is 10 mg by mouth once daily which can be increased to 20 mg once daily after one week. Adverse effects appear to be dose related and there is no available dosing data for adolescents and children. Escitalopram is extensively metabolized in the liver and thus therapy must be initiated and maintained at the lower end of the dosage range (i.e. 10 mg once daily) in patients with hepatic impairment. Specific guidelines for renal dosage adjustments are not available.

Clinical Efficacy Trials

The efficacy of escitalopram in the treatment of major depressive disorder has been based in part from the established effectiveness of racemic citalopram. In addition, two 8-week double-blinded, placebo-controlled, randomized studies were done to show it's effectiveness in the treatment of depression.

In the first study, 380 patients were randomized to escitalopram 10 mg/day or placebo. At the end of the 8 weeks, the escitalopram group showed a statistically significant improvement on the Montgomery Asberg Depression Rating Scale (MADRS) compared to placebo. In addition, in further by-

Table 1. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials[6]

Body System / Adverse Event	Percentage of Patients Reporting Event	
	Escitalopram (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder	9%	<1%
Impotence	3%	<1%
Anorgasmia	2%	<1%

week efficacy analyses, the effect of escitalopram was consistently larger than that for placebo beginning at week 1 as measured by the Clinical Global Impression Improvement Score.[5]

The second study was a fixed dose study of escitalopram 10 and 20 mg/day compared to placebo and citalopram 40 mg/day. This study was done in outpatients between the ages of 18 and 65 who met the DSM-IV criteria for major depressive disorder. The authors concluded that the escitalopram 10 and 20 mg/day treatment groups showed significantly greater and similar improvements compared to placebo on the MADRS. Furthermore, there was no significant difference in the incidence of adverse events between placebo and escitalopram 10 mg (79.0% vs. 70.5% respectively; $p=0.14$) or between citalopram 40 mg and escitalopram 20 mg (86.4% vs. 85.6% respectively; $p<0.01$).[6]

The long-term efficacy of escitalopram in major depressive disorder has not been evaluated. However, the longer term efficacy of racemic citalopram is well established. In two longer term studies, patients who responded to an initial 6 to 8 weeks of citalopram therapy were randomized to either continue racemic citalopram or to take placebo for up to 6 months. In both studies, patients who continued receiving racemic citalopram experienced significantly lower relapse rates.

In a third longer-term trial, patients who were diagnosed with recurrent major depressive disorder and in the past had responded to racemic citalopram were randomized to either continue their citalopram dose or to switch to placebo. Patients that continued receiving the racemic citalopram treatment experienced significantly lower relapse rates over the subsequent 72 weeks compared to those receiving placebo.

Table 2. Incidence of Common Adverse Events in Patients Receiving Placebo, 10 mg/day Escitalopram, or 20 mg/day Escitalopram[6]

Adverse Event	Placebo (N=311)	10 mg/day Escitalopram (N=310)	20 mg/day Escitalopram (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

Drug Interactions

In vitro studies indicate that CYP 3A4 and 2C19 are the main enzymes involved in the metabolism of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme should not significantly decrease escitalopram's clearance. However, in one study, subjects who received racemic citalopram 40 mg/day for 21 days concurrently with cimetidine 400 mg/day for 8 days experienced a 43% increase in citalopram's AUC. In addition, in vivo data showed that co-administration of escitalopram and a single dose of desipramine 50 mg (a substrate for CYP2D6) resulted in a 100% increase in the AUC of desipramine. Furthermore, co-administration of escitalopram 20 mg/day for 21 days resulted in an 82% increase in the AUC of metoprolol.

Adverse Effects

Adverse event information for escitalopram was collected in a double blind, placebo controlled trial. Seven hundred fifteen patients with major depressive disorder were exposed to escitalopram and 592 patients were exposed to placebo. The adverse events were obtained mainly by general inquiry. Similar types of events were grouped into a smaller number of standardized event categories. This information is summarized in Table 1.

Six percent of the patients in the escitalopram group and 2% in the placebo group discontinued therapy due to adverse events. As seen in Table 2, adverse events were dose dependent with the incidence for the 20 mg/day group being twice that of the 10 mg/day group.

Table 3. Cost Comparison Escitalopram

Pharmacy	10 mg/day	20 mg/day
Retail (chain)	69.19	73.09
Internet	64.04	66.83
Independent	71.71	74.49
Mean Price	68.31	71.47

Cost

The cost for a 30-day supply of escitalopram 10 mg and 20 mg tablets is summarized in Table 3.

Summary

Escitalopram is the active enantiomer of its parent compound citalopram. Its efficacy in the management of major depressive disorder was established in two 8-week double-blinded placebo-controlled randomized studies. Escitalopram appears to have a quicker onset of action compared to citalopram and it is effective in the treatment and maintenance of major depressive disorders with or without anxiety symptoms; however, superiority to citalopram has not been demonstrated.[8] Future comparative studies will help to establish its role in the treatment of major depressive disorder.

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Forteo™ (teriparatide [rDNA origin]) is the first in a new class of drugs called bone formation agents that work primarily to stimulate new bone by preferential stimulation of osteoblastic activity over osteoclastic activity. This form of recombinant human parathyroid hormone is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. The usual dosage is 20 mcg qd SQ (into thigh or abdominal wall). Use for more than 2 years is not recommended.

Abilify™ (aripiprazole) is a new agent used in the treatment of schizophrenia. It is a partial dopamine agonist with some 5-HT_{1A} agonistic and 5-HT_{2A} antagonistic activity. The usual initial adult dose is 10 mg once daily which can be increased after 2 weeks to a target of 15 mg once daily. Reduce dose to one-half of usual if concomitant 3A4 and 2D6 inhibitors. Double dose if concomitant 3A4 inducers.

Avage™ (tazarotene) cream 0.1% is a retinoic acid derivative used as an adjunct to a comprehensive skin care and sunlight avoidance program, in the mitigation of facial fine wrinkling, facial mottled hyper– and hypopigmentation, and benign facial lentigines. The usual dose for adults is a pea-sized (¼ inch or 5 mm diameter) amount to face (including eyelids) qhs.

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