Escitalopram Oxalate Oral Solution

Rx Only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use escitalopram oxalate safely and effectively. See full prescribing information for escitalopram oxalate

Escitalopram Oxalate Oral Solution

Initial U.S. Approval: 2002

Rx only

> **WARNING: Suicidality and Antidepressant Drugs**
>
> ***See full prescribing information for complete boxed warning.***
>
> **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Escitalopram oxalate is not approved for use in pediatric patients less than 12 years of age (5.1).**

----------INDICATIONS AND USAGE----------

Escitalopram oxalate oral solution is a selective serotonin reuptake inhibitor (SSRI) indicated for:

- Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12 to 17 years (1.1)
- Acute Treatment of Generalized Anxiety Disorder (GAD) in adults (1.2)

----------DOSAGE AND ADMINISTRATION----------

Escitalopram oxalate oral solution should generally be administered once daily, morning or evening with or without food (2.1, 2.2).

Indication	Recommended Dose
MDD (2.1)	
Adolescents (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
Adults (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
GAD (2.2)	
Adults (2.2)	Initial: 10 mg once daily Recommended: 10 mg once daily

- No additional benefits seen at 20 mg/day dose (2.1).
- 10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment (2.3).
- No dosage adjustment for patients with mild or moderate renal impairment. Use caution in patients with severe renal impairment (2.3).
- Discontinuing escitalopram oxalate oral solution: A gradual dose reduction is recommended (2.4).

----------DOSAGE FORMS AND STRENGTHS----------

- Oral solution: 1 mg per mL (3.2)

----------CONTRAINDICATIONS----------

- Monoamine Oxidase Inhibitors: Do not use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping escitalopram oxalate before starting an MAOI (4.1, 5.10).
- Pimozide: Do not use concomitantly (4.2, 7.10).
- Known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients (4.3).

----------WARNINGS AND PRECAUTIONS----------

- Clinical Worsening/Suicide Risk: Monitor for clinical worsening, suicidality and unusual change in behavior, especially, during the initial few months of therapy or at times of dose changes (5.1).
- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: Manage with immediate discontinuation and continuing monitoring (5.2).
- Discontinuation of Treatment with Escitalopram oxalate: A gradual reduction in dose rather than abrupt cessation is recommended whenever possible (5.3).
- Seizures: Prescribe with care in patients with a history of seizure (5.4).
- Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.5).
- Hyponatremia: Can occur in association with SIADH (5.6).
- Abnormal Bleeding: Use caution in concomitant use with NSAIDs, aspirin, warfarin or other drugs that affect coagulation (5.7).
- Interference with Cognitive and Motor Performance: Use caution when operating machinery (5.8).
- Use in Patients with Concomitant Illness: Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (5.9).

----------ADVERSE REACTIONS----------

Most commonly observed adverse reactions (incidence ≥ 5% and at least twice the incidence of placebo patients) are: insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue and somnolence, decreased libido, and anorgasmia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 866-495-1995, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Concomitant use with SSRIs, SNRIs or Tryptophan is not recommended (7.1).

Use caution when concomitant use with drugs that affect Hemostasis (NSAIDs, Aspirin, Warfarin) (7.6).

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus (8.1).

Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)

Pediatric Use: Safety and effectiveness of escitalopram oxalate has not been established in pediatric MDD patients less than 12 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

> **WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS**
>
> **Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of escitalopram oxalate or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Escitalopram oxalate is not approved for use in pediatric patients less than 12 years of age. [*See Warnings and Precautions: Clinical Worsening and Suicide Risk (5.1), Patient Counseling Information: Information for Patients (17.1), and Used in Specific Populations: Pediatric Use (8.4)*].**

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

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change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

1.2 Generalized Anxiety Disorder

Escitalopram oxalate oral solution is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults [*see Clinical Studies (14.2)*].

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

2 DOSAGE AND ADMINISTRATION

Escitalopram oxalate oral solution should be administered once daily, in the morning or evening, with or without food.

2.1 Major Depressive Disorder

Initial Treatment

Adolescents

The recommended dose of escitalopram oxalate oral solution is 10 mg once daily. A flexible-dose trial of escitalopram oxalate oral solution (10 to 20 mg/day) demonstrated the effectiveness of escitalopram oxalate oral solution *[see Clinical Studies (14.1)]*. If the dose is increased to 20 mg, this should occur after a minimum of three weeks.

Adults

The recommended dose of escitalopram oxalate oral solution is 10 mg once daily. A fixed-dose trial of escitalopram oxalate oral solution demonstrated the effectiveness of both 10 mg and 20 mg of escitalopram oxalate oral solution, but failed to demonstrate a greater benefit of 20 mg over 10 mg [*see Clinical Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing escitalopram oxalate oral solution 10 or 20 mg/day in adults patients with major depressive disorder who responded while taking escitalopram oxalate oral solution during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment [*see Clinical Studies (14.1)*]. Nevertheless, the physician who elects to use escitalopram oxalate oral solution for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Generalized Anxiety Disorder

Initial Treatment

Adults

The recommended starting dose of escitalopram oxalate oral solution is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Maintenance Treatment

Generalized anxiety disorder is recognized as a chronic condition. The efficacy of escitalopram oxalate oral solution in the treatment of GAD beyond 8 weeks has not been systematically studied. The physician who elects to use escitalopram oxalate oral solution for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.3 Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram oxalate oral solution should be used with caution in patients with severe renal impairment.

2.4 Discontinuation of Treatment with Escitalopram oxalate oral solution

Symptoms associated with discontinuation of escitalopram oxalate oral solution and other SSRIs and SNRIs have been reported [*see Warnings and Precautions (5.3)*]. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended [illegible]

Escitalopram oxalate oral solution contains escitalopram oxalate equivalent to 1 mg/mL esitalopram base.

4 CONTRAINDICATIONS

4.1 Monoamine oxidase inhibitors (MAOIs)

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated [*see Warnings and Precautions (5.10)*].

4.2 Pimozide

Concomitant use in patients taking pimozide is contraindicated [*see Drug Interactions (7.10)*].

4.3 Hypersensitivity to escitalopram or citalopram

Escitalopram oxalate oral solution is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in escitalopram oxalate oral solution.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1	
Age Range	**Drug-Placebo Difference in Number of Cases of Suicidability per 1000 patients Treated**
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer case

[illegible]

coded terms were uninformative or misleading) were reported at an incidence of at least 2% for escitalopram oxalate and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

Adults

The most commonly observed adverse reactions in escitalopram oxalate patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received escitalopram oxalate at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with escitalopram oxalate and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo-treated patients.

TABLE 2

Treatment-Emergent Adverse Reactions observed with a frequency of ≥ 2% and greater than placebo for Major Depressive Disorder

Adverse Reaction	Escitalopram oxalate	Placebo
	(N=715) %	(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%
Apetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinustis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

[1] Primarily ejaculatory delay.

[2] Denominator used was for males only (N=225 Escitalopram oxalate; N=188 placebo).

[3] Denominator used was for females only (N=490 Escitalopram oxalate; N=404 placebo).

Generalized Anxiety Disorder

Adults

The most commonly observed adverse reactions in escitalopram oxalate patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia.

Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received escitalopram oxalate 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with escitalopram oxalate and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo-treated patients.

TABLE 3

Treatment-Emergent Adverse Reactions observed with a frequency of ≥ 2% and greater than placebo for Generalized Anxiety Disorder

Adverse Reactions	Escitalopram oxalate	Placebo
	(N=429) %	(N=427) %
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1] Primarily ejaculatory delay.

[2] Denominator used was for males only (N=182 escitalopram oxalate; N=195 placebo).

[3] Denominator used was for females only (N=247 escitalopram oxalate; N=232 placebo).

Dose Dependency of Adverse Reactions

The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg escitalopram oxalate groups) was examined on the basis of the combined incidence of adverse reactions in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg escitalopram oxalate-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day escitalopram oxalate-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day escitalopram oxalate group with an incidence that was approximately twice that of the 10 mg/day escitalopram oxalate group and approximately twice that of the placebo group.

TABLE 4

Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder

Adverse Reaction	Placebo	10 mg/day	20 mg/day
	(N=311)	Escitalopram oxalate	Escitalopram oxalate
		(N=310)	(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%

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 5

Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Escitalopram oxalate	Placebo
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

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17.2 FDA-Approved Medication Guide

Medication Guide

Escitalopram Oxalate Oral Solution

⬆ DETACH BEFORE DISPENSING

Read the Medication Guide that comes with escitalopram oxalate oral solution before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about escitalopram oxalate oral solution?

Escitalopram oxalate oral solution and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **Escitalopram oxalate oral solution and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
  - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
  - Pay particular attention to such changes when escitalopram oxalate oral solution is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Escitalopram oxalate oral solution may be associated with these serious side effects:

2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions.
This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

3. Severe allergic reactions:

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

4. Abnormal bleeding: Escitalopram oxalate oral solution and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

5. Seizures or convulsions

6. Manic episodes:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

7. Changes in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

8. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop escitalopram oxalate oral solution without first talking to your healthcare provider. Stopping escitalopram oxalate oral solution too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is escitalopram oxalate oral solution?

Escitalopram oxalate oral solution is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. Escitalopram oxalate oral solution is also used to treat:

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)

Talk to your healthcare provider if you do not think that your condition is getting better with escitalopram oxalate oral solution treatment.

Who should not take escitalopram oxalate oral solution?

Do not take escitalopram oxalate oral solution if you:

- are allergic to escitalopram oxalate or citalopram hydrobromide or any of the ingredients in escitalopram oxalate oral solution. See the end of this Medication Guide for a complete list of ingredients in escitalopram oxalate oral solution.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - Do not take an MAOI within 14 days of stopping escitalopram oxalate oral solution.
  - Do not start escitalopram oxalate oral solution if you stopped taking an MAOI in the last 14 days.

People who take escitalopram oxalate oral solution close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)

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Size: 480 x 480 mm
Spec.: Printed on 40-45 GSM Bible paper, front & back side printing.
Pharma code Front 3067 Back 3068
Single colour : Pantone Black C
Note: Pharma code position and Orientation will be change based on folding size

How should I take escitalopram oxalate oral solution?

- Take escitalopram oxalate oral solution exactly as prescribed. Your healthcare provider may need to change the dose of escitalopram oxalate oral solution until it is the right dose for you.
- Escitalopram oxalate oral solution may be taken with or without food.
- If you miss a dose of escitalopram oxalate oral solution, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of escitalopram oxalate oral solution at the same time.
- If you take too much escitalopram oxalate oral solution, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking escitalopram oxalate oral solution?

Escitalopram oxalate oral solution can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how escitalopram oxalate oral solution affects you. Do not drink alcohol while using escitalopram oxalate oral solution.

What are the possible side effects of escitalopram oxalate oral solution?

Escitalopram oxalate oral solution may cause serious side effects, including all of those described in the section entitled "What is the most important information I should know about escitalopram oxalate oral solution?"

Common possible side effects in people who take escitalopram oxalate oral solution include**:**

- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Infection
- Yawning

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- difficult urination
- heavy menstrual periods
- possible slowed growth rate and weight change.

  Your child's height and weight should be monitored during treatment with escitalopram oxalate oral solution.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of escitalopram oxalate oral solution. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store escitalopram oxalate oral solution?

- Store escitalopram oxalate oral solution at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature].
- Keep escitalopram oxalate oral solution bottle closed tightly.

Keep escitalopram oxalate oral solution and all medicines out of the reach of children.

General information about escitalopram oxalate oral solution

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use escitalopram oxalate oral solution for a condition for which it was not prescribed. Do not give escitalopram oxalate oral solution to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about escitalopram oxalate oral solution. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about escitalopram oxalate oral solution that is written for healthcare professionals.

What are the ingredients in escitalopram oxalate oral solution?

Active ingredient: escitalopram oxalate

Inactive ingredients: anhydrous citric acid, glycerin, malic acid, methylparaben, natural peppermint flavor, non-crystallizing sorbital solution, propylene glycol, propylparaben, purified water and sodium citrate dihydrate.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Hetero Labs Limited
Jeedimetla, Hyderabad - 500 055, India

Revised 10/2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Weight Changes

Patients treated with escitalopram oxalate in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

Escitalopram oxalate and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with escitalopram oxalate treatment.

ECG Changes

Electrocardiograms from escitalopram oxalate (N=625) and placebo (N=527) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardic or bradycardic outliers, respectively). None of the patients in the escitalopram oxalate group had a QTcF interval >500 msec or a prolongation >60 msec compared to 0.2% of patients in the placebo group. The incidence of tachycardic outliers was 0.2% in the escitalopram oxalate and the placebo group. The incidence of bradycardic outliers was 0.5% in the escitalopram oxalate group and 0.2% in the placebo group.

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 113 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 4.5 (6.4) and 10.7 (12.7) msec for 10 mg and supratherapeutic 30 mg escitalopram given once daily, respectively. Based on the established exposure-response relationship, the predicted QTcF change from placebo arm (95% confidence interval) under the C_{max} for the dose of 20 mg is 6.6 (7.9) msec. Escitalopram 30 mg given once daily resulted in mean C_{max} of 1.7-fold higher than the mean C_{max} for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.

Other Reactions Observed During the Premarketing Evaluation of Escitalopram oxalate

Following is a list of treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with escitalopram oxalate for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in **Tables 2 & 3,** those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section (5)

Cardiovascular - hypertension, palpitation.

Central and Peripheral Nervous System Disorders - light-headed feeling, migraine.

Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis.

General - allergy, chest pain, fever, hot flushes, pain in limb.

Metabolic and Nutritional Disorders - increased weight.

Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness.

Psychiatric Disorders - appetite increased, concentration impaired, irritability.

Reproductive Disorders/Female - menstrual cramps, menstrual disorder.

Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache.

Skin and Appendages Disorders - rash.

Special Senses - vision blurred, tinnitus.

Urinary System Disorders - urinary frequency, urinary tract infection.

6.2 Post-Marketing Experience

Adverse Reactions Reported Subsequent to the Marketing of Escitalopram

The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.

Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.

Ear and labyrinth disorders: vertigo

Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.

Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance.

Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.

General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.

Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.

Immune System Disorders: allergic reaction, anaphylaxis.

Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.

Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.

Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.

Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.

Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.

Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.

Reproductive System and Breast Disorders: menorrhagia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.

Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.

Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs including escitalopram oxalate, and the potential for serotonin syndrome, caution is advised when escitalopram oxalate is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions (5.2)*]. The concomitant use of escitalopram oxalate with other SSRIs, SNRIs or tryptophan is not recommended.

7.2 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of escitalopram oxalate with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions (5.2)*].

7.3 CNS Drugs

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

7.4 Alcohol

Although escitalopram oxalate did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking escitalopram oxalate is not recommended.

7.5 Monoamine Oxidase Inhibitors (MAOIs)

[*see Contraindications (4.1) and Warnings and Precautions (5.10)*].

7.6 Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when escitalopram oxalate is initiated or discontinued.

7.7 Cimetidine

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

7.8 Digoxin

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

7.9 Lithium

Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when escitalopram oxalate and lithium are coadministered.

7.10 Pimozide and Citalopram

In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

7.11 Sumatriptan

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised.

7.12 Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

7.13 Warfarin

Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

7.14 Carbamazepine

Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

7.15 Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

7.16 Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

7.17 Ritonavir

Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

7.18 CYP3A4 and -2C19 Inhibitors

In vitro studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

7.19 Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

7.20 Metoprolol

Administration of 20 mg/day escitalopram oxalate for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of escitalopram oxalate and metoprolol had no clinically significant effects on blood pressure or heart rate.

7.21 Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and escitalopram.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy : Teratogenic Effects:

Pregnancy Category C

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m²] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m² basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m² basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m² basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to escitalopram oxalate and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*].

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with escitalopram oxalate during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration (2.1)*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

8.2 Labor and Delivery

The effect of escitalopram oxalate on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Escitalopram is excreted in human breast milk. Limited data from women taking 10 to 20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when escitalopram oxalate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of escitalopram oxalate has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of escitalopram oxalate has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder *[see Clinical Studies (14.1)]*. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Safety and effectiveness of escitalopram oxalate has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder.

Decrease appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as escitalopram oxalate.

8.5 Geriatric Use

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of escitalopram oxalate in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of escitalopram oxalate between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of escitalopram oxalate cannot be ruled out.

SSRIs and SNRIs, including escitalopram oxalate, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Hyponatremia (5.6)*].

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology (12.3)*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration (2.3)*].

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse and Dependence

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of racemic citalopram is low. Escitalopram oxalate has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with escitalopram oxalate did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate escitalopram oxalate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In clinical trials of escitalopram, there were reports of escitalopram oxalate overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, escitalopram oxalate overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported.

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

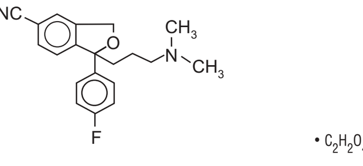
10.2 Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for escitalopram oxalate.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

11 DESCRIPTION

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor (SSRI).Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414.40.

Escitalopram oxalate occurs as a fine, white to slightly-yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane.

Escitalopram oxalate is available as an oral solution.

Escitalopram oral solution contains escitalopram oxalate equivalent to 1 mg/mL escitalopram base. It also contains the following inactive ingredients: anhydrous citric acid, glycerin, malic acid, methylparaben, natural peppermint flavor, non-crystallizing sorbital solution, propylene glycol, propylparaben, purified water and sodium citrate dihydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

12.2 Pharmacodynamics

In vitro and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic (5-HT $_{1to7}$) or other receptors including alpha- and beta-adrenergic, dopamine (D_{1to5}), histamine (H_{1to3}), muscarinic (M_{1to5}), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

12.3 Pharmacokinetics

The single-and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27 to 32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2 to 2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.

The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1to7}$) or other receptors including alpha- and beta-adrenergic, dopamine (D_{1to5}), histamine (H_{1to3}), muscarinic (M_{1to5}), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Subgroups

Age

Adolescents - In a single dose study of 10 mg escitalopram, AUC of escitalopram decreased by 19%, and C_{max} increased by 26% in healthy adolescent subjects (12 to 17 years of age) compared to adults. Following multiple dosing of 40 mg/day citalopram, escitalopram elimination half-life, steady-state C_{max} and AUC were similar in patients with MDD (12 to 17 years of age) compared to adult patients. No adjustment of dosage is needed in adolescent patients.

Elderly - Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients [see Dosage and Administration (2.3)].

Gender - Based on data from single- and multiple-dose studies measuring escitalopram in elderly, young adults, and adolescents, no dosage adjustment on the basis of gender is needed.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients [*see Dosage and Administration (2.3)*].

Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2C9, -2C19, and -2E1. Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. *See Drug Interactions (7.18)* for more detailed information on available drug interaction data.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with racemic citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day. Similar findings were not present in rats receiving 24 mg/kg/day of racemic citalopram for two years, in mice receiving up to 240 mg/kg/day of racemic citalopram for 18 months, or in dogs receiving up to 20 mg/kg/day of racemic citalopram for one year.

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs

In a one-year toxicology study, 5 of 10 beagle dogs receiving oral racemic citalopram doses of 8 mg/kg/day died suddenly between weeks 17 and 31 following initiation of treatment. Sudden deaths were not observed in rats at doses of racemic citalopram up to 120 mg/kg/day, which produced plasma levels of citalopram and its metabolites demethylcitalopram and didemethylcitalopram (DDCT) similar to those observed in dogs at 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, racemic DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

Adolescents

The efficacy of escitalopram oxalate as an acute treatment for major depressive disorder in adolescent patients was established in an 8-week, flexible-dose, placebo-controlled study that compared escitalopram oxalate 10 to 20 mg/day to placebo in outpatients 12 to 17 years of age inclusive who met DSM-IV criteria for major depressive disorder. The primary outcome was change from baseline to endpoint in the Children's Depression Rating Scale - Revised (CDRS-R). In this study, escitalopram oxalate showed statistically significant greater mean improvement compared to placebo on the CDRS-R.

The efficacy of escitalopram oxalate in the acute treatment of major depressive disorder in adolescents was established, in part, on the basis of extrapolation from the 8-week, flexible-dose, placebo-controlled study with racemic citalopram 20 to 40 mg/day. In this outpatient study in children and adolescents 7 to 17 years of age who met DSM-IV criteria for major depressive disorder, citalopram treatment showed statistically significant greater mean improvement from baseline, compared to placebo, on the CDRS-R; the positive results for this trial largely came from the adolescent subgroup.

Two additional flexible-dose, placebo-controlled MDD studies (one escitalopram oxalate study in patients ages 7 to 17 and one citalopram study in adolescents) did not demonstrate efficacy.

Although maintenance efficacy in adolescent patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Adults

The efficacy of escitalopram oxalate as a treatment for major depressive disorder was established in three, 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder. The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS).

A fixed-dose study compared 10 mg/day escitalopram oxalate and 20 mg/day escitalopram oxalate to placebo and 40 mg/day citalopram. The 10 mg/day and 20 mg/day escitalopram oxalate treatment groups showed statistically significant greater mean improvement compared to placebo on the MADRS. The 10 mg and 20 mg escitalopram oxalate groups were similar on this outcome measure.

In a second fixed-dose study of 10 mg/day escitalopram oxalate and placebo, the 10 mg/day escitalopram oxalate treatment group showed statistically significant greater mean improvement compared to placebo on the MADRS.

In a flexible-dose study, comparing escitalopram oxalate, titrated between 10 and 20 mg/day, to placebo and citalopram, titrated between 20 and 40 mg/day, the escitalopram oxalate treatment group showed statistically significant greater mean improvement compared to placebo on the MADRS.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

In a longer-term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week, open-label treatment phase with escitalopram oxalate 10 or 20 mg/day, were randomized to continuation of escitalopram oxalate at their same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined by having a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram oxalate experienced a statistically significant longer time to relapse compared to those receiving placebo.

14.2 Generalized Anxiety Disorder

The efficacy of escitalopram oxalate in the acute treatment of Generalized Anxiety Disorder (GAD) was demonstrated in three, 8-week, multicenter, flexible-dose, placebo-controlled studies that compared escitalopram oxalate 10 to 20 mg/day to placebo in adult outpatients between 18 and 80 years of age who met DSM-IV criteria for GAD. In all three studies, escitalopram oxalate showed statistically significant greater mean improvement compared to placebo on the Hamilton Anxiety Scale (HAM-A).

There were too few patients in differing ethnic and age groups to adequately assess whether or not escitalopram oxalate has differential effects in these groups. There was no difference in response to escitalopram oxalate between men and women.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.2 Oral Solution:

5 mg/5 mL, peppermint flavor (240 mL), NDC 31722-569-24

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

17.1 Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe escitalopram oxalate

General Information about Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with escitalopram oxalate and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for escitalopram oxalate. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking escitalopram oxalate.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Warnings and Precautions (5.1)*].

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of **escitalopram oxalate** and triptans, tramadol or other serotonergic agents [*see Warnings and Precautions (5.2)*].

Abnormal Bleeding

Patients should be cautioned about the concomitant use of escitalopram oxalate and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding [*see Warnings and Precautions (5.7)*].

Concomitant Medications

Since escitalopram is the active isomer of racemic citalopram, the two agents should not be coadministered. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Continuing the Therapy Prescribed

While patients may notice improvement with escitalopram oxalate therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Interference with Psychomotor Performance

Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that escitalopram oxalate therapy does not affect their ability to engage in such activities.

Alcohol

Patients should be told that, although escitalopram oxalate has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of escitalopram oxalate and alcohol in depressed patients is not advised.

Pregnancy and Breast Feeding

Patients should be advised to notify their physician if they

- become pregnant or intend to become pregnant during therapy.
- are breastfeeding an infant.

Need for Comprehensive Treatment Program

Escitalopram oxalate is indicated as an integral part of a total treatment program for MDD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all adolescents with this syndrome. Safety and effectiveness of escitalopram oxalate in MDD has not been established in pediatrics patients less than 12 years of age. Antidepressants are not intended for use in the adolescent who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe antidepressant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

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