Cymbalta (duloxetine) was recently introduced in the United States. Unlike the selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine), which are relatively serotonin-specific antidepressants, Cymbalta has a dual mechanism of action. Presumably, it works by altering the neurotransmission of both serotonin and norepinephrine, two important neurotransmitters in the brain.

During neurotransmission, neurotransmitters are released by one neuron into the space between that neuron and the next neuron. The neurotransmitters come into contact with specific sites on the surface membrane of neurons called receptors. From there, the chemical is transformed into an electrical impulse that travels down the neuron, causing further release of neurotransmitters. This process of neurotransmission is repeated along a chain of neurons. During neurotransmission, after neurotransmitters are released and the chemical signal is transferred to neurons, the neurotransmitters are recaptured back into brain cells by a process known as reuptake. By blocking the neurotransmitters from going back into the neurons from where they were released, the antidepressant can amplify the effects of the neurotransmitter.

Cymbalta exerts its antidepressant effect principally by blocking the reuptake of serotonin and norepinephrine. This action is similar to that of the SSRIs, but notably different in that Cymbalta also inhibits the reuptake of norepinephrine. Through reuptake inhibition, Cymbalta boosts serotonin and norepinephrine neurotransmission. For this reason, Cymbalta is called a serotonin-norepinephrine reuptake inhibitor (SNRI). Depression and other mental disorders may be caused by abnormally low levels (or abnormal neurotransmission) of serotonin, norepinephrine, or both. This abnormality may in turn produce changes in affected areas of the brain, resulting in psychiatric symptoms such as panic disorder or generalized anxiety disorder. When neurotransmission is improved by the antidepressant, the affected areas of the brain are restored to normal functioning, reducing the symptoms of the illness.

Cymbalta was approved by the FDA for the treatment of major depressive disorder. The use of a medication for its approved indications is called its labeled use. In clinical practice, physicians often prescribe medications for unlabeled (“off-label”) uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of these medications for these unapproved indications. Physicians may prescribe Cymbalta to treat panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social phobia, and other conditions.
Dosing Information

The starting dosage for Cymbalta is 40 mg/day, administered in divided doses of 20 mg twice a day. If adequate response is not achieved in 10–14 days, the dosage is increased to 60 mg/day given either once a day or in doses of 30 mg twice daily.

Common Side Effects

The most common side effects reported with Cymbalta are nausea, vomiting, constipation, dry mouth, dizziness, increased sweating (e.g., night sweats), fatigue, and insomnia. Side effects generally occur soon after starting the medication or when increasing the dosage. If side effects become intolerable, the physician may decrease the dosage to allow the individual to adjust to the medication before increasing it again slowly.

Sexual side effects, including delayed orgasm in women and retarded ejaculation in men, occur with Cymbalta at about the same rate as with the other SNRI antidepressant, Effexor (venlafaxine), but at a rate lower than the 50%–60% rate reported with the SSRIs.

Cymbalta does not appear to induce weight gain. In clinical trials, patients taking Cymbalta gained less weight than those taking placebo (sugar tablets).

Adverse Reactions and Precautions

Patients taking normal dosages of Cymbalta may develop mild elevation of blood pressure (hypertension). The increase in blood pressure is usually modest, and very few patients have to discontinue Cymbalta because of hypertension. Generally, lowering the dosage will normalize blood pressure. For this reason, the patient’s blood pressure should be checked before starting Cymbalta and routinely during therapy as a precautionary measure, especially for individuals with preexisting hypertension or those with a history of heart disease.

Cymbalta may worsen uncontrolled narrow-angle glaucoma, an eye disorder caused by increased intraocular pressure. Therefore, Cymbalta should be avoided in patients with poorly controlled narrow-angle glaucoma.

Abrupt discontinuation of Cymbalta may precipitate withdrawal symptoms, including dizziness, nausea, headache, vomiting, irritability, and nightmare. Withdrawal symptoms may be avoided by tapering the dosage gradually before discontinuation.

Cymbalta’s pharmacological action may cause urinary difficulty and hesitancy. Men with an enlarged prostate may be particularly prone to this adverse effect.

Use in Pregnancy and Breastfeeding: Pregnancy Category C

Cymbalta has not been tested in women to determine its safety in pregnancy. The effects of the medication on the developing fetus are unknown. However, newborn babies exposed to antidepressants such as Cymbalta and SSRIs late in the third trimester developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Women who are pregnant or may become pregnant should discuss this with their physician. Some women may experience a recurrence of their depression when they stop their antidepressant. In these circumstances it may be necessary to restart the medication or seek an alternative medication or treatment.

Nursing mothers should not take Cymbalta because small amounts will pass into breast milk and be ingested by the baby. If stopping the antidepressant is not an alternative, breastfeeding should not be started or should be discontinued.
Possible Drug Interactions

Cymbalta, like many other medications, is metabolized in the liver. The combined use with certain medications may result in adverse drug interactions because one medication may alter the blood levels of the other. Reported drug interactions with Cymbalta are few. The significant drug interactions that have been reported with Cymbalta are summarized in the table below.

| Other medications, including herbal supplements (such as St. John’s wort), that boost serotonin can result in excessive levels of the neurotransmitter serotonin when combined with Cymbalta and produce a toxic syndrome known as serotonin syndrome. The early signs of serotonin syndrome are restlessness, confusion, tremors, flushing, and involuntary muscle jerks. If the medications are not stopped, the individual may develop more life-threatening complications resulting in muscle disorders, high fever, respiratory problems, clotting problems, and destruction of red blood cells that can lead to acute renal failure. Hence, patients taking Cymbalta should be alert to the possible signs of serotonin syndrome, which require immediate medical attention and discontinuation of the serotonin-boosting medications.

Antidepressants known as monoamine oxidase inhibitors (MAOIs) should not be taken together with Cymbalta, because the combination may potentially produce a toxic reaction that includes elevated temperature, high blood pressure, and extreme excitation and agitation. Patients should consult their physician or pharmacist before taking any new medications, including over-the-counter medications and herbal supplements, with Cymbalta.

Patients taking Cymbalta should avoid alcohol or should consume it in moderation because the combination may worsen depression. Smoking may significantly reduce the serum levels of Cymbalta by as much as one-third. Individuals who smoke while taking Cymbalta may require higher dosages to achieve therapeutic levels.

<table>
<thead>
<tr>
<th>Luvox (fluvoxamine)</th>
<th>Luvox can inhibit the metabolism of Cymbalta. This can result in significantly elevated levels of Cymbalta, potentially increasing adverse side effects. When a patient’s medication is switched to Cymbalta after discontinuation of Luvox, the treatment should begin with a smaller-than-normal dosage of Cymbalta, because significant levels of Luvox may still be present in the body.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro (ciprofloxacin)</td>
<td>Cipro and antibiotics in this family can inhibit the metabolism of Cymbalta and elevate its levels, potentially increasing the likelihood of adverse side effects.</td>
</tr>
<tr>
<td>Tagamet (cimetidine)</td>
<td>Tagamet can inhibit the metabolism of Cymbalta and elevate its levels, potentially increasing adverse side effects.</td>
</tr>
<tr>
<td>Paxil (paroxetine) and Prozac (fluoxetine)</td>
<td>Paxil and Prozac, two selective serotonin reuptake inhibitors (SSRIs), are potent inhibitors of the enzyme that metabolizes Cymbalta. This can result in significantly elevated levels of Cymbalta, potentially increasing adverse effects. When a patient’s medication is switched to Cymbalta after discontinuation of Paxil or Prozac, treatment should begin with a smaller-than-normal dosage of Cymbalta, because significant levels of the SSRI may still be present in the body.</td>
</tr>
</tbody>
</table>
**Overdose**

There is limited clinical experience with Cymbalta overdose, and no cases of fatal acute overdose have been reported. In contrast with overdoses involving tricyclic and MAOI antidepressants, overdose with Cymbalta should be much less dangerous, especially when it is taken alone. However, overdoses often involve multiple medications, and the combination of medications may present more serious complications. The combination of central nervous depressants (e.g., alcohol, narcotics, benzodiazepines) and Cymbalta can be lethal, and death is usually from respiratory depression.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

**Special Considerations**

Most cases of major depression can be treated successfully, usually with medication, psychotherapy, or both. The combination of psychotherapy and antidepressants is very effective in treating moderate to severe depression. The medications improve mood, sleep, energy, and appetite, while therapy strengthens coping skills, deals with possible underlying issues, and improves thought patterns and behavior. Cymbalta may also be very beneficial for treating anxiety.

In general, antidepressants alone help about 60%–70% of those taking them. Although a few individuals may experience some improvement from antidepressants by the end of the first week, most people do not see significant benefits from their antidepressants until after 3–4 weeks, and it can sometimes take as long as 8 weeks for the medication to produce its full effects. Thus it is critical that patients continue to take their antidepressant long enough for the medication to be beneficial and that patients not get discouraged and stop their medication prematurely if they do not feel better immediately.

The controversial issue of suicide and antidepressants has prompted the FDA to ask manufacturers of some antidepressants, particularly the SSRIs, to provide warnings in their package insert that the risk of suicide may be increased in depressed individuals (especially children) the first several weeks after beginning an antidepressant. However, studies have found that when more people in a community are taking antidepressants, the suicide rate is lower. The risk of suicide is inherent in depression and may persist until the individual responds to treatment. Depressed individuals who are at risk for suicide should be closely watched at the outset of therapy, and any signs of suicidal or violent behavior should be immediately reported to the physician or a mental health provider.

- **Warning**: Always let your physician or a family member know if you have suicidal thoughts. Notify your psychiatrist or your family physician whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.
- Do not discontinue Cymbalta abruptly. To prevent unpleasant discontinuation symptoms, Cymbalta requires gradual tapering before completely stopping the medication.
- If you miss a dose, take it as soon as possible, within 2–3 hours of the scheduled dosing. If it is close to your next scheduled dose, skip the missed dose and continue on your regular dosing schedule, but do not take double doses.
- Cymbalta should be swallowed whole and not crushed or chewed, nor should the capsule be opened and sprinkled in food.
- Cymbalta may be taken with or without food.
- Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication.
- Keep your medication out of reach of children.

*If you have any questions about your medication, consult your physician or pharmacist.*