Lamotrigine (Lamictal) was originally developed as an antiseizure (antiepileptic) drug for treatment of epilepsy. Shortly after it was introduced, patients reported improvement in their mood independent of the drug’s anticonvulsant activity. This finding spurred investigation of lamotrigine for treatment of mood disorders. Early clinical studies, however, failed to show that lamotrigine was effective in treating acute mania, but subsequent clinical trials demonstrated that it was beneficial in delaying the time to occurrence of the next depressive or manic episode in bipolar disorder. In 2003, the U.S. Food and Drug Administration (FDA) approved lamotrigine for maintenance treatment of bipolar disorder, specifically to delay the time to occurrence of mood episodes (mania, hypomania, depression, and mixed episodes). When lamotrigine is used to treat mood disorders, it is considered a mood stabilizer rather than an anticonvulsant.

Lamotrigine may also be used for other treatments not approved by the FDA. The use of a medication for its FDA-approved indications is called its labeled use. In clinical practice, however, practitioners may prescribe medications for unapproved indications (off-label uses) when published clinical studies indicate the efficacy, and the standards of medical practice support the safety, of those treatments. Lamotrigine’s off-label uses, for example, may include treatment-resistant depression, schizoaffective disorder, and prevention of migraine headaches.

Clinical studies have shown that lamotrigine is effective in delaying the onset of mood episodes (e.g., depression, mania, hypomania, mixed episodes) in maintenance treatment of bipolar disorder. Lamotrigine can be used alone or in combination with another mood stabilizer, such as lithium. If it is used with valproate (e.g., Depakote), however, certain precautions must be followed to minimize the risk of developing a potentially severe rash (see section “Adverse Reactions and Precautions”). Lamotrigine may be effective in treating patients with rapid-cycling bipolar disorder (four or more episodes of mania, hypomania, or depression a year). Patients whose mania is accompanied by irritability rather than euphoria may benefit from lamotrigine. Moreover, lamotrigine may be very helpful for treating or preventing bipolar depression. Patients receiving lamotrigine alone for treatment of bipolar depression showed marked improvement in depressive symptoms.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available brands</td>
<td>Lamictal, Lamictal XR, Lamictal ODT</td>
</tr>
<tr>
<td>Available strengths and formulations</td>
<td>25-mg, 50-mg, 100-mg, 150-mg, and 200-mg tablets (Lamictal)</td>
</tr>
<tr>
<td></td>
<td>25-mg, 50-mg, 100-mg, 200-mg, 250-mg, and 300-mg extended-release tablets (Lamictal XR)</td>
</tr>
<tr>
<td></td>
<td>25-mg, 50-mg, 100-mg, and 200-mg orally disintegrating tablets (Lamictal ODT)</td>
</tr>
<tr>
<td>Available in generic</td>
<td>Yes, all formulations and strengths</td>
</tr>
</tbody>
</table>
The recommended starting dosage of lamotrigine is 25 mg/day with the immediate-release tablet (or orally disintegrating tablets) on weeks 1 and 2, increasing to 50 mg/day by week 3, 100 mg/day by week 5, and 200 mg/day by week 6. By week 7, most patients are taking a target dosage of 200 mg/day. Some patients require a higher dosage if they are taking carbamazepine (Tegretol) or other drugs that enhance the metabolism of lamotrigine. In these situations, the starting dosage is 50 mg/day on weeks 1 and 2, increasing to 100 mg/day by week 3, 200 mg/day by week 5, 300 mg/day by week 6, and up to 400 mg/day by week 7. At higher dosages, the total daily dosage should be administered in divided doses of two or three times daily. The immediate-release form may be converted to once-a-day dosing with lamotrigine extended-release tablets.

If the patient is currently taking valproate (e.g., Depakote), lamotrigine should be introduced slowly; valproate may double the blood levels of lamotrigine and cause toxicity. The recommendation is to start with 25 mg every other day for weeks 1 and 2, increase to 25 mg/day on week 3, 50 mg/day on week 5, and the target dosage of 100 mg/day by week 6.

Common side effects associated with lamotrigine include sedation, headache, impaired coordination, unsteadiness when walking, double vision (diplopia), and rash (nonserious). Gastrointestinal side effects include nausea, vomiting, abdominal cramping, dry mouth, and constipation. Weight gain is generally not problematic with lamotrigine and may be used sometimes to counteract other medications that promote weight gain, such as antipsychotics, lithium, and valproate.

Lamotrigine can cause serious, life-threatening skin rashes, including a form called Stevens-Johnson syndrome, which is characterized by painful blistering of the skin and mucous membranes due to death (necrosis) of skin cells. The syndrome is thought to be caused by a hypersensitivity reaction to the medication, but it is associated with other causes as well, such as infections. The incidence of rashes is highest in children receiving lamotrigine for epilepsy; the incidence is very low in adults (1/1,000). The skin reaction is caused by individual susceptibility, and there are no factors that can predict one’s susceptibility to the rash or the severity of rash associated with lamotrigine. Patients should stop taking lamotrigine at the first sign of rash and contact their practitioner, but if the rash is accompanied by malaise, sore throat, and fever, they should seek immediate medical attention at an emergency department for evaluation.

Lamotrigine should not be abruptly discontinued; it should be gradually tapered before discontinuation. The exception, however, is with the appearance of rash associated with lamotrigine, especially when accompanied by malaise or fever; in this case the patient should stop taking the drug immediately and seek medical attention.

Patients taking lamotrigine should not consume alcohol because the combination may increase sedation and drowsiness. Moreover, the sedative effects of alcohol may act as a depressant, obscuring the therapeutic effects of lamotrigine and complicating treatment. Lamotrigine may cause drowsiness and impair alertness, especially at the start of therapy. Patients should use caution when driving or performing tasks that require alertness.

There are no well-controlled studies of lamotrigine in pregnant women to determine the risks in pregnancy. However, animal studies suggest that lamotrigine can have risk because it has been shown to decrease the
concentration of folic acid, a B vitamin, in rats. Decreased fetal concentrations of folic acid are known to have harmful effects in animals and humans. In an ongoing registry conducted by the manufacturer to follow women who were exposed only to lamotrigine during pregnancy, the current data suggest there may be a small increase in the rate of birth defects associated with lamotrigine, but the extent of the risk is unclear.

Lamotrigine should be considered during pregnancy only if it is critical to the health of the woman and the potential benefits outweigh the potential risk in the fetus. Women of childbearing age should be cautioned of the potential hazards to the fetus if they become pregnant while taking this drug. Patients can obtain more information regarding risk during pregnancy from the North American Antiepileptic Drug (AED) Pregnancy Registry by calling toll-free 1-888-233-2334. This must be done by the patients themselves. Patients taking the medication during pregnancy are encouraged to enroll in the registry. Information about the registry can also be found on the following Web site: www.aedpregnancyregistry.org.

Nursing mothers should not take lamotrigine because it passes into breast milk and may be harmful to the baby when ingested. If stopping the drug is not an alternative, breast-feeding should not be started or should be discontinued.

**POTENTIAL DRUG INTERACTIONS**

Lamotrigine undergoes metabolism in the liver and is eliminated. The combined use of lamotrigine with certain other drugs may cause significant drug interactions that can alter its blood levels. Drugs that increase the metabolism of lamotrigine, possibly significantly decreasing its concentration and therapeutic effectiveness, include estrogen-containing oral contraceptives, estrogens (hormone replacement), carbamazepine, phenobarbital, primidone, phenytoin, protease inhibitors (lopinavir/ritonavir, atazanavir/ritonavir), and rifampin. The dosage for lamotrigine thus need to be increased if any of these drugs are also being coadministered, and the dosage will need to be adjusted down if the other drug is stopped. Lamotrigine has an effect on oral contraceptives containing progestins (e.g., levonorgestrel), and especially progestin-only products; patients should be aware that lamotrigine can decrease progestin levels and result in contraceptive failure.

Of particular concern is a lamotrigine and valproate (e.g., Depakene, Depakote) interaction. In the presence of valproate, lamotrigine concentrations may increase by about twofold, increasing the risk of toxicity, especially the risk of severe rash. Therefore, when lamotrigine is added to valproate, it must be introduced gradually, with smaller doses, and the maximum recommended total dosage should not exceed 100 mg/day.

**OVERDOSE**

Depending on the amount ingested, overdose with lamotrigine can be fatal. Non-life-threatening symptoms of overdose include dizziness, nystagmus (jerky eye movements), ataxia (impaired coordination in voluntary movements), headache, and somnolence. In severe cases, overdose may result in heart block (interference with conduction of the heartbeat), seizures, decreased level of consciousness, and coma. In small children, the lethal dose may be lower than for an adult of average size.

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 along as well because the information on the prescription label can be helpful to the treating practitioner in determining the number of pills ingested.

The American Association of Poison Control Centers (www.aapcc.org) can also be contacted via their helpline at 1-800-222-1222, and they can provide the location of the local poison center.

**TREATMENT SUMMARY**

- If you miss a dose, take it as soon as possible. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.
• Do not discontinue lamotrigine without consulting your practitioner. Lamotrigine should be discontinued gradually by tapering the dose. Stopping the medication abruptly may trigger discontinuation symptoms.
• Take lamotrigine immediately after meals or with food to decrease stomach upset.
• Do not break, crush, or chew lamotrigine tablets. Swallow the tablet whole.
• Place the orally disintegrating tablet (Lamictal ODT) on your tongue and allow it to dissolve without chewing; do not swallow the tablet whole.
• Stop taking lamotrigine and contact your practitioner immediately if you develop a rash.
• Seek immediate medical assistance if you develop fever, sore throat, swelling of your tongue or face, skin pain, and widespread, blistering skin rashes, as these symptoms may be indicative of a serious skin reaction to lamotrigine.
• Inform your practitioner if you start any new medication, including oral contraceptives and over-the-counter supplements.
• Lamotrigine may cause sedation and drowsiness, especially during initiation of therapy, and impair your alertness. Use caution when driving or performing tasks that require alertness. Avoid alcohol when taking lamotrigine because alcohol may intensify these effects.
• Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
• Keep your medication out of the reach of children. Acute overdose in small children is very dangerous.

If you have any questions about your medication, consult your medical practitioner or pharmacist.

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