LAMOTRIGINE

LAMITOR 50 / LAMITOR-100
50mg and 100mg Tablet
Antiepileptic

WARNING:
"At the first sign of rash, discontinue medication" due to increased incidence of Stevens Johnson syndrome associated with the drug."

FORMULATION
Each tablet contains:
Lamotrigine..... 50 and 100 mg

PRODUCT DESCRIPTION
Lamotrigine (Lamitor 50) 50 mg and Lamotrigine (Lamitor-100) 100 mg are light yellow colored, round, flat beveled edge, uncoated with bisecting line on one side of tablet.

CLINICAL PHARMACOLOGY

Mechanism of Action
The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.
One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In virto pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).
Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor-Mediated Activity: Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC for lamotrigine effects on NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM. The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

Pharmacodynamics

Folate Metabolism
In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys
Lamotrigine accumulated in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding
Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular
In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease, patients taking concomitant medications that inhibit glucuronidation).

Pharmacokinetics
Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. It is widely distributed in the body and is 55 % reported to be about 55% bound to plasma protein. It is extensively metabolized in the liver and excreted almost entirely in the urine, principally as glucuronide conjugate. It slightly induces its own metabolism and the half-life steady state is reported to be about 24 hours. Lamotrigine is distibuted in the breast milk.

INDICATIONS
Monotherapy and adjunctive treatment of partial seizures and primary and secondary generalized tonic-clonic seizures, seizures associated with Lennox-Gestaut syndrome. It is also used in the prophylaxis of bipolar disorder in adults.

DOSAGE AND ADMINISTRATION

For Epilepsy
As monotherapy: ADULTS and CHILDREN > 12 years - Initial adult dose as monotherapy is 25 mg once daily by mouth for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by 50mg/day every 1 to 2 weeks to usual maintenance doses of 225 mg to 375mg daily, given 2 divided doses. **CHILDREN 2 to 12 years** - Initial dose is 300 mcg/kg bodyweight daily in 1 or 2 divided doses for 2 weeks followed by 600 mcg/kg body weight in 2 divided doses for 2 weeks; thereafter the dose is increased by 600 mcg/kg body weight daily every 1 to 2 weeks to usual maintenance dose of 4.5 to 7.5 mg/kg body weight daily (maximum of 300mg daily in 2 divided doses). Maintenance dose in patients less than 30kg may need to be increased by as much as 50%, based on clinical response. Or as prescribed by the physician.
Add on therapy (without valproate) : ADULTS - 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks, thereafter the dose is increased by 100 mg/day every 1 to 2 weeks to usual maintenance doses of 300 to 500 mg daily given in 2 divided doses. **CHILDREN** - Initial dose is 600 mcg/kg body weight daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg body weight in two divided doses for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg body weight every 1 to 2 weeks to a usual maintenance dose of 5 to 15 mg/kg body weight (maximum 400 mg/day) given in 2 divided doses. Maintenance dose in patients less than 30kg may need to be increased by as much as 50%, based on clinical response. Or as prescribed by the physician.
Add on therapy (with valproate) : ADULTS - Initial dose is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by 25 to 50 mg/day every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily with valproate alone and 100 to 400mg daily with valproate and other drugs that induce glucoronidation, given as a single dose or in 2 divided doses. **CHILDREN** - Initial dose is 150 mcg/kg body weight once daily for 2 weeks followed by 300 mcg/kg once daily for 2 weeks, thereafter the dose is increased by 300 mcg/kg every 1 to 2 weeks to usual maintenance dose of 1 mg to 5 mg/kg body weight (maximum 200mg/day in 1 or 2 divided doses) which may be given once daily or in 2 divided doses and 1mg to 3mg/kg/day for those patients taking valproate alone as an add on. Maintenance dose in patients less than 30kg may need to be increased by as much as 50%, based on clinical response. Or as prescribed by the physician.
NOTE: If the calculated dose for children lies between 1 and 2 mg then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be administered if the calculated dose is less than 1 mg.

Usual Adjunctive Maintenance Dose
In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital or primidone without valproate, maintenance doses of adjunctive lamotrigine as high as 700mg/day have been used. In patients receiving valproate alone, maintenance doses of adjunctive lamotrigine as high as 200mg/day have been used.

Conversion from Adjunctive Therapy to Monotherapy
The goal of the transition regimen is to attempt to maintain seizure control while mitigating the risk of serious rash associated with the rapid titration of lamotrigine.
The recommended maintenance dose of lamotrigine as monotherapy is 500 mg/day given in 2 divided doses.
To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations for lamotrigine should not be exceeded.

Conversion from Adjunctive Therapy with Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy with Lamotrigine
After achieving a dose of 500 mg/day of lamotrigine, the concomitant enzyme-inducing anti-epileptic drugs should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant antiepileptic drug is based on experience gained in the controlled monotherapy clinical trial.

Conversion from Adjunctive Therapy with Valproate to Monotherapy with Lamotrigine
The conversion regimen involves 4 steps outlined below.

Steps	Lamotrigine	Valproate
1	Achieve a dose of 200mg/day	Maintain establish stable dose
2	Maintain 200 mg/day	Decrease dose by decrements no greater than 500 mg/day/week and then maintain the dose of 500 mg/day for 1 week
3	Increase to 300 mg/day and maintain for 1 week	Simultaneously decrease to 250 mg/day and maintain for 1 week
4	Increase by 100mg/day every week to achieve maintenance dose of 500 mg/day	Discontinue

Conversion from Adjunctive Therapy with Antiepileptic Drugs other than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy with Lamotrigine
No specific dosing guidelines can be provided for conversion to monotherapy with lamotrigine with anti-epileptic drugs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate.

For Bipolar Disorder
As Monotherapy : The initial recommended dosage is 25 mg once daily which is gradually increased to 200 mg daily over 6 weeks. Dosages over 200 mg / day as monotherapy are not recommended.
For patients taking valproate: 25 mg every other day and the target dosage is 100 mg /day from week 6. In recipients of carbamazepine (or other enzyme inducing drugs) the initial recommended dosage is 50 mg once daily which is gradually increased up to 400 mg / day from week 7. Dosages > 50 mg /day can be given once daily or as two divided doses.
Dosage Adjustments to Lamotrigine in Adults with Bipolar Disorder Following Discontinuation of Psychotropic Medications

Week	Discontinuation of Psychotropic Drugs (excluding Valproate, Carbamazepine, Phenytoin, Phenobarbital, or Primidone)	After Discontinuation of Valproate	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, or Primidone
		Current Dose of Lamotrigine (mg/day) 100	Current Dose of Lamotrigine (mg/day) 400
1	Maintain current dose of Lamotrigine	150	400
2	Maintain current dose of Lamotrigine	200	300
3 Onward	Maintain current dose of Lamotrigine	200	200

CONTRAINDICATION
It is contraindicated in patients known to be hypersensitive to Lamotrigine.

WARNINGS AND PRECAUTIONS
- Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash includes co-administration with valproate, exceeding recommended Initial dose of lamotrigine and exceeding recommended dose escalation for lamotrigine.

Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. Lamotrigine should be discontinued
at the first sign of rash, unless the rash is clearly not drug related.

- Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms, may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure,blood dyscrasias, or acute multiorgan failure. Lamotrigine should be discontinued if alternate etiology for this reaction is not found.
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia) may occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding.
- Antiepileptic drugs, including lamotrigine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any anti epileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Therapy with lamotrigine increases the risk of developing aseptic meningitis. Monitor for signs and symptoms of meningitis. Symptoms include headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia, myalgia, chills, altered consciousness, and somnolence.
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct.
- Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine. Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking lamotrigine. During the week of inactive hormone preparation (pill-free week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse reactions consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.
- Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in 1 controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown. Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.
- Particular care is needed in addition of lamotrigine to a multidrug regimen that includes valproate.

Withdrawal

As with other anti-epileptic drugs, lamotrigine should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in adults with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. Unless safety concerns require a more rapid withdrawal, the dose of lamotrigine should be tapered over a period of at least 2 weeks (approximately 50% reduction per week).

PREGNANCY AND LACTATTION

As with other antiepileptic drugs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. Lamotrigine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses that were also maternally toxic. The no effect doses for embryo fetal developmental toxicity in mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or less than (rats) the human dose of 400 mg/day on a body surface area (mg/m) basis.

In a study in which pregnant rats were administered lamotrigine (oral doses of 5 or 25 mg/kg) during the period of organogenesis and offspring were evaluated postnatally, behavioral abnormalities were observed in exposed offspring at both doses. The lowest effect dose for developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a mg/m basis. Maternal toxicity was observed at the higher dose tested.

When pregnant rats were administered lamotrigine (oral doses of 5, 10, or 20 mg/kg) during the latter part of gestation, increased offspring mortality (including stillbirths) was seen at all doses. The lowest effect dose for peri/postnatal developmental toxicity in rats is less than the human dose of 400 mg/day on a mg/m basis. Maternal toxicity was observed at the 2 highest doses tested. Lamotrigine decreases fetal folate concentrations in rat, an effect known to be associated with adverse pregnancy outcomes in animals and humans.

Lamotrigine is present in milk from lactating women taking lamotrigine. Data from multiple small studies indicate that lamotrigine plasma levels in human milk-fed infants have been reported to be as high as 50% of the maternal serum levels. Neonates and young infants are at risk for high serum levels because maternal serum and milk levels can rise to high levels postpartum if lamotrigine dosage has been increased during pregnancy but not later reduced to the pre-pregnancy dosage. Lamotrigine exposure is further increased due to the immaturity of the infant glucuronidation capacity needed for drug clearance.

Events including apnea, drowsiness, and poor sucking have been reported in infants who have been human milk-fed by mothers using lamotrigine; whether or not these events were caused by lamotrigine is unknown. Human milk-fed infants should be closely monitored for adverse events resulting from lamotrigine. Measurement of infant serum levels should be performed to rule out toxicity if concerns arise. Human milk-feeding should be discontinued in infants with lamotrigine toxicity. Caution should be exercised when lamotrigine is administered to a nursing woman.

DRUG INTERACTIONS

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of lamotrigine is enhanced by the enzyme inducers carbamazepine, phenytoin, phenobarbital, primidone, and inhibited by valproate. Use with rifampicin significantly increased the clearance of lamotrigine.

Protease inhibitors lopinavir/ritonavir and atazanavir/lopinavir decrease lamotrigine exposure by approximately 50% and 32%, respectively.

Lamotrigine is an inhibitor of renal tubular secretion via organic cationic transporter 2 (OCT2) proteins. This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Coadministration of lamotrigine with OCT2 substrates with anarrow therapeutic index (e.g., dofetilide) is not recommended.

Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine.

ADVERSE EFFECTS

Skin rashes may occur during therapy with lamotrigine, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine. Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial edema and, rarely hepatic dysfunction, leucopenia, and thrombocytopenia have also been reported in conjunction with rashes as part of a hypersensitivity syndrome.

Other adverse effects include angioedema and photosensitivity, diplopia, blurred vision, and conjunctivitis, and dizziness, drowsiness, insomia, headache, ataxia, nystagmus, tremor, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, confusion, somnolence, rhinitis, pharyngitis, infection, diarrhea, abdominal pain, back pain and xerostomia.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of lamotrigine.

STORAGE AND CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABLITY

Lamotrigine (Lamitor 50) 50 mg Tablet - PVC/Alu Blister Pack of 10's (Box of 30's) - DRP-2948
Lamotrigine (Lamitor-100) 100 mg Tablet - Blister Pack of 10's (Box of 30's) - DRP-2757

DATE OF FIRST AUTHORIZATION

July 3, 2007 - Lamitor 50
February 8, 2008 - Lamitor-100

DATE OF REVISION

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torrent PHARMA

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