For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only.

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LAMITOR 25 MG TABLETS
LAMITOR 50 MG TABLETS
LAMITOR 100 MG TABLETS

(Lamotrigine Tablets, 25, 50 and 100mg)

DESCRIPTION

Lamitor 25 mg Tablets: Light yellow coloured, round, flat, uncoated tablets with bisecting line on one side (Thickness1.9 - 2.3mm, average weight 85.0mg and diameter 6.35mm).

Lamitor 50 mg Tablets: Light yellow coloured, round, flat, uncoated tablets with bisecting line on one side (Thickness 2.5 - 2.9mm, average weight 170.0mg and diameter 7.93mm).

Lamitor 100 mg Tablets: Light yellow coloured, round, flat, uncoated tablets with bisecting line on one side (Thickness 3.0 - 3.4mm, average weight 340.0mg and diameter 10.31mm).

Lamotrigine is an antiepileptic drug of phenyltriazine class. It's chemical name is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3, 5-diamine, its molecular formula is $C_9H_7Cl_{12}N_5$ and molecular weight is 256.09. Lamotrigine is white to pale cream coloured powder and has a Pka of 5.7. It is very slightly soluble in water (0.17 mg/ml at 25^oC) and slightly soluble in 0.1 M HCl (4.1 mg/ml at 25^oC).

COMPOSITION

LAMITOR 25 MG TABLETS: Each tablet contains 25 mg lamotrigine.

LAMITOR 50 MG TABLETS: Each tablet contains 50 mg lamotrigine.

LAMITOR 100 MG TABLETS: Each tablet contains 100 mg lamotrigine.

MODE OF ACTION:

Results of pharmacological studies suggest that LAMITOR is a use-dependent blocker of voltage gated sodium channels. It produces a use and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

PHARMACOKINETICS:

Absorption:

Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur 2.5 ± 1.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics is linear up to 450 mg; the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within and individual concentrations vary very little.

Distribution:

Binding to plasma proteins is about 55%. It is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 L/kg.

Metabolism:

UDP-glucuronyl transferases have been identified as the enzyme responsible for metabolism of lamotrigine.

There is no evidence that Lamotrigine affects the pharmacokinetics of other AEDs and data suggests that interactions between Lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination:

The mean steady state clearance in healthy adults is 39±14 ml/min. Clearance of Lamotrigine is primarily metabolic with subsequent elimination of glucuronide-concentrated materials in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in feces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.

The half-life of Lamotrigine is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with enzyme inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with sodium valproate alone. The half-life of Lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme inducing drugs such as carbamazepine, phenytoin, phenobarbital and primidone and increased to a mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone.

Mean pharmacokinetic parameters in adult patients with epilepsy or healthy volunteers

Adult study population	Number of subjects	T max (hour)	Elimination half life (hour)	Apparent plasma clearance (ml/min/kg)
Patients taking enzyme inducing antiepileptic drugs (EIAEDs)				
Single dose lamotrigine	24	2.3 (6.4-30.4)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple dose lamotrigine	17	12.6 (7.5-23.1)	12.6(7.5-23.1)	1.21(0.66-1.82)
Patients taking EIAEDs + VPA)				
Single dose lamotrigine	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Healthy volunteers				
Single dose lamotrigine	179	2.2 (0.215-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple dose lamotrigine	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)

(Numbers in parenthesis indicate the range of individual volunteer/patient values across studies)

Special populations:

Patients with renal insufficiency There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicates that lamotrigine pharmacokinetics are little affected but plasma concentration of the major glucuronide metabolite increases almost eight fold due to reduced renal clearance.

Hepatic disease: The pharmacokinetics of Lamotrigine following a single 100 mg dose of lamotrigine were evaluated in 24 subjects with moderate to severe hepatic dysfunction and compared with 12 subjects without hepatic impairment. The median apparent clearance of Lamotrigine was 0.31, 0.24, or 0.10 ml/kg/min in patients with grade A, B, C (Child Pugh classification) hepatic impairment, respectively compared top 0.34 ml/kg/min in healthy volunteers. Median half-life was 36, 60 or 110 hours in patients with Grade A, B, C hepatic impairment respectively, versus 32 hours in healthy subjects.

Pediatric patients:

Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five years. The half life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme inducing drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone.

Elderly:

In a single dose study (150 mg of lamotrigine) the pharmacokinetics of Lamotrigine in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance=61 ml/min) were similar to those of young, healthy volunteers in other studies.

INDICATIONS

Adults

LAMITOR is indicated for use as adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalized seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome.

CONTRA-INDICATIONS

LAMITOR is contra-indicated in the following circumstances:

Individuals with known hypersensitivity to lamotrigine.

WARNINGS & PRECAUTIONS

Potential for an increase in risk of suicidal thoughts or behaviours.

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of LAMITOR.

Patients receiving LAMITOR should be closely monitored and changes in hepatic, renal and clotting parameters looked for. Patients should be warned to consult their doctors immediately if rashes or flu-like symptoms associated with hypersensitivity develop, especially within the first month of starting treatment with LAMITOR. Withdrawal of LAMITOR therapy should be considered if unexplained rashes, fever, flu-like symptoms, drowsiness or worsening of seizure control occur.

Dosage recommendations should not be exceeded to minimise the risk of developing rash requiring withdrawal of therapy. Abrupt withdrawal of LAMITOR may provoke rebound seizures. The risk may be reduced by tapering off the withdrawal of LAMITOR over a period of two weeks.

The weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

Skin Reactions

Adverse skin reactions have been reported, which have generally occurred within the first 8 weeks of starting LAMITOR. Although the majority of rashes usually resolve when LAMITOR is discontinued, irreversible scarring and cases of associated death have been reported. A mild rash may subside even with continuation of LAMITOR therapy, however, close monitoring is essential. Less frequently, serious and potentially life-threatening skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported especially in children and in patients using valproate (see SIDE-EFFECTS). Isolated cases have been reported after prolonged treatment (6 months).

The estimated incidence of serious skin rashes in adults is 1 in 1000. The risk is higher in children than in adults. Available data suggest the incidence in children requiring hospitalisation ranges from 1 in 300 to 1 in 100

In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy.

The overall risk of rash appears to be strongly associated with:

-High initial doses of LAMITOR and exceeding the recommended dose escalation of LAMITOR (see DOSAGE AND DIRECTIONS FOR USE).

- Concomitant use of valproate, which increases the mean half-life of LAMITOR nearly two-fold (see DOSAGE AND DIRECTIONS FOR USE).

As it cannot be predicted reliably which rashes will prove to be life-threatening, all patients (adults and children) who develop a rash should be promptly evaluated and LAMITOR withdrawn immediately unless the rash is clearly not drug related.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, pruritus, facial oedema, abnormalities of the blood and liver and thrombocytopenia. The syndrome shows a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multiorgan failure. It is important that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and LAMITOR therapy discontinued if an alternative aetiology cannot be immediately established.

INTERACTIONS

Enzyme-inducing agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) enhance the metabolism of LAMITOR leading to an increased clearance and subsequent reduction of the elimination half-life of LAMITOR. Concomitant use of valproic acid increases the half-life and plasma concentrations of LAMITOR due to competition for hepatic glucuronidation. Plasma concentrations of valproic acid may decrease slightly when LAMITOR is added.

There is no evidence that LAMITOR causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. LAMITOR may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

LAMITOR is a week inhibitor of dihydrofolate reductase hence there is a possibility of interference with folate metabolism during long-term therapy. However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in advance effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required.

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following introduction of Lamotrigine, These events usually resolve when the dose of carbamazepine is reduced.

PREGNANCY AND LACTATION

Fertility:

There is not experience of the effect of Lamitor on Human Fertility.

Pregnancy:

There are insufficient data available on the use of Lamitor in human pregnancy to evaluate its safety. As with most drugs, Lamitor should not be used in pregnancy unless in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Lactation:

There is limited information on the use of Lamotrigine in lactation.

Preliminary data indicates that it passes in to the breast milk usually of the order of 40-60% of the serum concentration.

In a small number of infants known to have been breast fed, the serum concentration of Lamotrigine reached level at which pharmacological effects may occur.

Potential benefits of breast-feeding should be weighed against potential risk of adverse effects occurring in the infants.

DOSAGE AND DIRECTIONS FOR USE

Dosage in epilepsy monotherapy

Adults (over 12 years of age)

The initial LAMITOR dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 – 100 mg every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 – 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of Lamotrigine to achieve the desired response. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded.

Recommended dosage escalation for adults (over 12 years of age) on monotherapy

Weeks 1 & 2	Weeks 3 & 4	Maintenance Dose
25 mg (once daily)	50 mg (once daily)	100 – 200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50 – 100 mg every 1 – 2 weeks

Dosage in add-on therapy

Adults (over 12 years of age)

In patients taking valproate with/without any other antiepileptic drug (AED), the initial LAMITOR dose is 25mg every alternate day for two weeks, followed by 25mg once a day for two weeks. Thereafter the dose should be increased by a maximum of 25-50mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses. In those patients taking concomitant AEDs or other medications (see interactions) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial LAMITOR dose is 50 mg once a day for two weeks, followed by 100mg/day given in two divided doses for two weeks. The dose should be increased by a maximum of 100mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400mg/day given in two divided doses. Some patients have required 700mg/day of LAMITOR to achieve the desired response. In those patients taking oxcarbazepine without any other inducers or inhibitors of lamotrigine glucuronidation, the initial LAMITOR dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response in 100 to 200 mg/day given once a day or as two divided doses.

Recommended dosage escalation for adults (over 12 years of age) on combined drug therapy

	Weeks 1 & 2	Weeks 3 & 4	Maintenance Dose
Valproate with/without any other AEDs	12.5mg (given 25mg alternate days)	25mg (once a day)	100-200mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 25-50mg every 1-2 weeks.
Enzyme inducing AEDs* with/without other AEDs (except valproate)	50mg (once a day)	100mg (two divided doses)	200-400mg (two divided doses). To achieve maintenance, doses may be increased by 100mg every 1-2 weeks.
*e.g. phenytoin, carbamazepine, phenobarbitone and primidone			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.			

Elderly (over 65 years of age):

No dosage adjustment from recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population.

Hepatic impairment:

Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

SIDE EFFECTS :

Skin rashes occur in up to 10% of patients taking Lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of Lamotrigine treatment in 2% of patients.The rash usually maculopapular in appearance generally appears within 8 weeks of starting treatment and resolves on withdrawal of Lamotrigine.

Rarely, serious potentially life threatening skin rashes ,including Stevens Johnsons syndrome and Toxic epidermal necrolysis (Lyell Syndrome) have been reported.Although the majority recover on drug withdrawal,some patients experience irreversible scarring and there have been cases of associated death.The overall risk of rash appears to be strongly associated with:

--High initial dose of Lamotrigine and exceeding the recommended dose. Escalation of Lamotrigine therapy (see dosage)

---Concomittant use of Valproate

Rash has also been reported as part of hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may rarely lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestation of hypersensitivity may be present even if rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and Lamitor discontinued if an alternative aetiology can not be established. Adverse experience reported during Lamitor monotherapy trials includes headache, tiredness, rash, nausea, dizziness, drowsiness and insomnia.

Other adverse experiences have included diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, headache, tiredness, gastrointestinal disturbances, irritability/aggression, agitation, confusion and hallucination.

Movement disorder such as unsteadiness, ataxia, nystagmus, and tremor have also been reported. There have been reports that Lamitor may worsen parkinsonism symptoms, in patients with pre-existing Parkinson's disease and isolated reports of Extrapyramidal effects and choreoathlosis in patients without this underlying condition.

Elevation of liver function tests and rarely hepatic dysfunction including hepatic failure may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms and signs

Acute ingestion of doses in excess of 10 – 20 times the maximum therapeutic doses has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.

Treatment

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

STORAGE

Store below 25^oC. Protect from heat & light.

PRESENTATION

Lamitor 25mg, 50mg and 100mg tablets are packed in Alu-PVC blister of 10 tablets. Such blisters containing 10 tablets are packed into a carton of 10's, 30's , 50's and 100's.

Not all presentations may be available locally.

DATE OF REVISION:

August 18, 2015

torrent PHARMA

Manufactured by :

TORRENT PHARMACEUTICALS LTD.

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