For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only. 8051290-8883

LAMITOR

(Lamotrigine tablets, 25mg/50mg/100mg)

DESCRIPTION :

LAMITOR is an antiepileptic drug (AED) of phenyltriazine class. Its molecular formula is $C_9H_7Cl_2N_5$ and molecular weight is 256.09. It is white to pale cream coloured powder and has a Pka of 5.7. It is very slightly soluble in water and slightly soluble in HCl.

CLINICAL PHARMACOLOGY :

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. 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. Binding to plasma proteins is about 55%.

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.

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.

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	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 : 12 volunteers with chronic renal failure (mean creatinine clearance 13ml/min range 6-23) and another 6 individuals undergoing hemodialysis were each given a single 100 mg dose of Lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis) and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range 5.6-35.1) of the amount of Lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session.

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 to 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 : The pharmacokinetics of Lamotrigine following a single dose of 2mg/kg were evaluated in two studies of pediatric patients with epilepsy (n=25 for patients aged 10 months to 5.3 years and n=19 for patients aged 5-11 years) all patients were receiving concomitant therapy with other AEDs. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in the following table

Pediatric study population	Number of subjects	T max (h)	Elimination half life (hour)	Apparent plasma clearance (ml/min/kg)
Ages 10 months to 5.3 years Patients taking enzyme inducing antiepileptic drugs (EIAEDs)	10	3.0(1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.71-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Age 5-11 years Patients taking EIAEDs	7	1.6(1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs + VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89(0.39-1.93)
Ages 13-18 years Patients taking EIAEDs	11			1.3
Patients taking EIAEDS + VPA	8			0.5
Patient taking VPA Only	4			0.3

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

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 :

Adjunctive use : LAMITOR is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in generalized seizures of Lennox Gastaut syndrome in pediatric and adult patients.

Monotherapy use: LAMITOR is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single EIAED.

Safety and effectiveness of LAMITOR have not been established 1) as initial monotherapy 2) for conversion to monotherapy from non enzyme inducing AEDs (e.g. Valproate) or 3) for simultaneous conversion to monotherapy from two or more concomitant AEDs.

Safety and effectiveness in patients below the age group of 16 other than those with Lennox Gastaut syndrome have not been established.

CONTRA-INDICATIONS, WARNINGS AND PRECAUTIONS :

Contra-indications : LAMITOR is contra-indicated in individuals with known hypersensitivity to Lamotrigine or its ingredients.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMITOR, IT IS NOT POSSIBLE TO PREDICI RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY LAMITOR SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS TRE RASH IS CLEARLY NOT DRUG RELATED DISCONTINUATION OF TREATMENT MIGHT NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

Precautions : Available data suggest that exceeding the recommended dose at the initiation of Lamotrigine therapy may be associated with an increased incidence of rash requiring withdrawal of therapy.

When other anti-epileptic drugs (AEDs) are added on Lamitor consideration should be given to the effect this may have on Lamotrigine pharmacokinetics

It is recommended that the physician closely monitor (including hepatic, renal and clotting parameters) patients who acutely develop any combination of unexplained rash, fever, flu-like symptoms, drowsiness or worsening of seizure control, especially within the first month of starting treatment with Lamotrigine.

As with other anti-epileptic drugs, abrupt withdrawal of Lamotrigine may provoke rebound seizures. This risk may be avoided by tapering the withdrawal of Lamotrigine over a period of 2 weeks. In end stage renal failure patients, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised if situation warrants administration of Lamotrigine in these patients.

The results of a wide range of mutagenicity tests indicate that Lamotrigine does not present a genetic risk to man.

Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

Administration of Lamotrigine did not impair fertility in animal reproductive studies. There is no experience of the effect of Lamotrigine on human fertility.

WARNING :

Severe skin rash including Stevens-Johnson syndrome and rarely Toxic Epidermal Necrolysis has been reported in some cases. Because the rate of serious rash is greater in pediatric patients than in adults, it bears emphasis that **Lamotrigine is approved only for use in pediatric patients below the age of 16 years who have seizures associated with the Lennox Gastaut syndrome.** Lamotrigine should be discontinued at the first sign of rashes. The risk is more in cases where (1) Sodium Valproate is co-administered (2) dose administered exceeds the recommended initial and total daily dose.

USE IN PREGNANCY AND LACTATION :

Lamotrigine is a week inhibitor of dihydrofolate reductase. There is a theoretical risk of human fetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicity studies with lamotrigine in animals at doses in excess of the human therapeutic doses showed no teratogenic effects. There are insufficient data available on the use of lamotrigine in pregnant women to evaluate its safety. **Lamotrigine should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.**

Preliminary, data indicates that lamotrigine passes into breast milk in concentrations usually of the order of 40-45% of the plasma concentration. In the small number of infants known to have been breastfed, the dose of lamotrigine received was calculated to be approximately 0.06-0.75 mg/kg/24 hours, and no adverse experience was reported.

SIDE AND ADVERSE EFFECTS :

Adverse experiences reported during Lamotrigine monotherapy trials include headache, tiredness, rash, nausea, dizziness, drowsiness and insomnia.

The rash reported in approximately 2% cases is usually maculopapular in appearance generally appears within 4 weeks of starting treatment and resolves on withdrawal of lamotrigine. Severe skin reactions including angioedema, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis have been reported.

Rash has also been reported as part of a hypersensitivity syndrome associated with a viable pattern of systemic symptoms including fever, malaise, flu like symptoms drowsiness, lymphadenopathy, facial oedema and rarely, hepatic dysfunction and abnormalities of the blood, such as leucopenia and thrombocytopenia. The syndrome shows a wide spectrum of clinical severity and may, rarely, have a fatal outcome. In the majority of patients symptoms resolve on prompt discontinuation of lamotrigine therapy.

All patients who develop a rash should be promptly evaluated and consideration should be given to the withdrawal of lamotrigine.

Other adverse experiences reported when lamotrigine is added on to standard anti-epileptic drug regimens have included diplopia, blurred vision, dizziness, drowsiness, headache, unsteadiness, tiredness, gastrointestinal disturbance, irritability/aggression, tremor, agitation, confusion and haematological abnormalities including neutropenia and leucopenia.

DRUG INTERACTIONS :

Anti-epileptic agents which induce drug-metabolizing enzymes in the liver (such as phenytoin, carbamazepine, phenobarbitone and primidone) enhance the metabolism of Lamotrigine and may increase dose requirements.

Sodium valproate, which competes with Lamotrigine for drug metabolizing enzymes in the liver, reduces the metabolism of Lamotrigine. There is no evidence that Lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolizing enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Although changes in the plasma concentrations of other anti-epileptic drugs have been reported in a few patients, however controlled studies have shown no evidence that Lamotrigine affects the plasma concentrations of concomitant anti-epileptic drugs. Evidence from in vitro studies indicates that Lamotrigine does not displace other anti-epileptic drugs from protein binding sites.

DOSAGE AND ADMINISTRATION :

Pediatric patients who weigh less than 17 kg should not receive LAMITOR because therapy cannot be initiated using the dosing guidelines given below.

LAMITOR added to AED regimen containing VPA in patients 2-12 years of age

Week 1 & 2
0.15 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg. If the initial calculated daily dose of LAMITOR is 2.5 to 5 mg then 5 mg LAMITOR should be taken on alternate days for the first 2 weeks.
Week 3 & 4
0.3 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg.
Maintenance dose :
1 to 5 mg/kg/day in one or two divided doses (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to nearest 5 mg and add this amount to the previously administered daily dose.

LAMITOR added to EIAEDs (Without VPA) in patients 2 to 12 years of age

Week 1 & 2
0.6 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg.
Week 3 & 4
1.2 mg/kg/day in two divided doses, rounded down to the nearest 5 mg.
Maintenance dose :
5 to 15 mg/kg/day (maximum 400 mg/day two divided doses). To achieve the usual maintenance dose subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to nearest 5 mg and add this amount to the previously administered daily dose.

Patients over 12 years of age : Recommended guidelines for LAMITOR added to VPA and EIAEDs are given in the following tables.

LAMITOR added to AED regimen containing VPA in patients over 12 years of age

Week 1 & 2
25 mg every other day
Week 3 & 4
25 mg every day
Maintenance dose :
100-400 mg/day in one or two divided doses. To achieve the usual maintenance dose subsequent doses should be increased by 25-50 mg/day every 1 to 2 weeks. The usual maintenance dose in patients adding LAMITOR to VPA alone ranges from 100-200 mg/day.

LAMITOR added to EIAEDs (Without VPA) in patients over 12 years of age

Week 1 & 2
50 mg /day
Week 3 & 4
100 mg every day in two divided doses
Maintenance dose :
300-500 mg/day in two divided doses. To achieve the usual maintenance dose subsequent doses should be increased by 100 mg/day every 1 to 2 weeks.

Conversion from a single EIAED to monotherapy with LAMITOR in patients ≥ 16 years of age : The conversion regimen involves two steps, first LAMITOR is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level, in the second step the EIAED is gradually withdrawn over period of 4 weeks. The recommended maintenance dose of LAMITOR as monotherapy is 500 mg/kg/day given in two divided doses. Because of an increased risk of rash, the recommended initial dose and subsequent dose escalation of LAMITOR should not be exceeded.

Usual maintenance dose : In patients receiving multidrug regimens employing EIAEDs without VPA, maintenance dose of LAMITOR may be as high as 700 mg/day have been used. In patients receiving VPA alone maintenance dose of LAMITOR as high as 200 mg/day have been used.

LAMITOR added to other AEDS than EIAEDs and VPA : The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMITOR cannot be predicted. Therefore no specific dosing guidelines can be provided. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent.

Use in hepatic impaired patients : The experience is limited. Based on a clinical pharmacology study on 24 patients with moderate to severe liver dysfunction the following general recommendations can be made. Initial, escalation, and maintenance doses should be generally be reduced by approximately 50% in patients with moderate (Child Pugh grade B) and 75% in patients with severe (Child Pugh grade C) hepatic impairment. Escalation and maintenance should be adjusted based on the clinical response.

Patients with renal function impairment: Initial doses of LAMITOR should be based on patients AED regimen, reduced maintenance doses may be effective for patients with significant renal function impairment. LAMITOR should be used with caution in these patients.

Use in the elderly : There is limited information on the use of Lamotrigine in elderly patients. To date, there is no evidence to suggest that the response of this age group differs from that in the young. However, elderly patients should be treated cautiously.

OVERDOSAGE, TOXICITY AND TREATMENT :

Symptoms and signs: Ingestion of between 1.35 and 4 g lamotrigine has been reported. Clinical consequences were not severe, signs and symptoms included nystagmus, ataxia, dizziness, somnolence, headache and vomiting.

A patient who ingested a dose calculated to be between 4 and 5 g lamotrigine was admitted to hospital with coma lasting 8-12 hours followed by recovery over the next 2 to 3 days. A further patient who ingested 5.6 g lamotrigine was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours.

Treatment : In the event of an overdosage, the patient should be hospitalized, observed and given appropriate supportive therapy. Gastric lavage may be indicated.

STORAGE :

Store Below 30°C

PRESENTATION :

LAMITOR tablets are supplied in blister pack of 10 tablets, each containing lamotrigine 25 mg, 50 mg or 100 mg.

torrent PHARMA

Manufactured by :
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