Lomogin

TABLETS

(Lamotrigine) USP

COMPOSITION

Lomogin 25mg:

Each tablet contains: Lamotrigine (USP).....25mg

Lomogin 50mg:

Each tablet contains: Lamotrigine (USP).....50mg

Lomogin 100mg:

Each tablet contains: Lamotrigine (USP).....100mg

INDICATIONS

ADULTS: Lomogin 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.

CHILDREN: Lomogin is indicated as adjunctive therapy in the treatment of epilepsy, for partial seizures and generalized seizures including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome, initial monotherapy treatment in newly diagnosed paediatric patients is not recommended.

After epileptic control has been achieved during adjunctive therapy, concomitant anti-epileptic drugs (AED's) may be withdrawn and patients continued on Lomogin monotherapy.

DOSAGE

DOSAGE IN MONOTHERAPY

ADULTS (OVER 12 YEARS OF AGE): The initial Lomogin dose in monotherapy is 25mg once a day for two weeks, followed by 50mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100mg every 1-2 week until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200mg/day given once a day or as two divided doses. Some patients have required 500mg/day of Lomogin to achieve the desired response.

Recommended dose escalation for adults (over 12 Years of age) on monotherapy.

WEEKS 1-2	WEEKS 3-4	MAINTENANCE DOSE
25 mg (Once a day)	50 mg (Once a day)	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

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded.

DOSAGE IN ADD ON-THERAPY

ADULTS (OVER 12 YEARS OF AGE): In patients taking valproate with / without any other anti-epileptic drug (AED), the initial Lomogin 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 100-200mg/day given once a day or in two divided doses. In those patients taking enzyme inducing (AED's) with / without other AEDs (except valproate), the initial Lomogin dose is 50mg once a day for two weeks, followed by 100mg/ day given in two divided doses for two weeks. Thereafter, 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 Lomogin to achieve the desired response.

Recommended dose 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.			

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded.

CHILDREN (2 TO 12 YEARS OF AGE): To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to body weight, do not equate to whole tablets the dose to be administer is that equal to the lower number of whole tablets. In patients taking Valproate with / without any other AED, the initial Lomogin dose is 0.2mg/kg body weight/ day given once a day for two weeks, followed by 0.5mg/kg/day once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.5-1mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5mg/kg/day given once a day or in two divided doses, with a maximum of 200mg/ day. In those patients taking enzyme inducing AEDs with/without other AEDs (except Valproate), the initial Lomogin dose is 2mg/kg body weight/ day given in two divided doses for two weeks, followed by 5mg/kg/ day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 2.0mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15mg/kg/day given in two divided doses, with a maximum of 400mg/day.

Recommended dose escalation for children aged 2-12 years (total daily dose in mg/kg body weight/day) on combined drug therapy.

	WEEKS 1-2	WEEKS 3-4	MAINTENANCE DOSE
Valproate with/ Without any Other AEDs	0.2mg/kg (once a day)	0.5mg/kg (once a day)	1-5mg/kg (once a day or two divided doses) To achieve maintenance, doses may be increased by 0.5-1mg/kg every 1-2 weeks, to a maximum of 200mg/day
Enzyme inducing AEDs* with/ Without other AEDs (except Valproate)	2mg/kg (two divided doses)	5mg/kg (two divided doses)	5-15mg/kg (two divided doses) To achieve maintenance, doses may be increased by 2-3mg/kg every 1 -2 weeks, to a maximum of 400mg/kg
* e. 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.			

** Note: If the calculated daily dose is 2.5-5mg, then 5mg Lomogin may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 2.5mg, then Lomogin should not be administered. Because of risk of rash the initial dose and subsequent dose escalation should not be exceeded. When concomitant antiepileptic drugs are withdrawn to actual Lomogin paediatric monotherapy consideration should be given to the effect this may have on Lamotrigine Pharmacokinetics and the dose be adjusted appropriately. It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

CHILDREN AGED LESS THAN 2 YEARS: There is insufficient information on the use of Lomogin in children aged less than 2 years.

THE ELDERLY: There is limited information on the use of Lomogin 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.

CONTRA-INDICATIONS

Lomogin is contraindicated in individuals with known hypersensitivity to Lamotrigine.

PRECAUTIONS AND WARNINGS

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of Lamotrigine treatment. The majority of rashes are mild and self limiting, however serious, potentially life threatening skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. The approximate incidence of serious skin rashes in adults is 1 in 1000. The risk is higher in children than in adults. Incidence in children requiring hospitalization 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. Additionally the overall risk of rash appears to be strongly associated with:

- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy.
- Concomitant use of valproate, which increases the mean half-life of Lamotrigine nearly two fold.

All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine 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, facial oedima and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. 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 Lomogin discontinued if an alternative aetiology cannot be established. As with other AEDs, abrupt withdrawal of Lomogin may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, dose of Lomogin should be gradually decreased over a period of 2 weeks. When concomitant antiepileptic drugs are withdrawn to achieve Lomogin monotherapy or other antiepileptic drugs (AEDs) are added-on to Lomogin monotherapy consideration should be given to the effect this may have on Lamotrigine Pharmacokinetics. Lomogin is a weak 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.

In single dose studies in subjects with end stage renal failure, plasma concentrations of Lamotrigine were not significantly altered. However, accumulation of the glucuronid metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure. Lomogin is cleared primarily by metabolism in the liver. No studies have been carried out in patients with significant impairment of hepatic function. Severe convulsive seizures including status epilepticus may

lead to rhabdomyolysis; multiorgan dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of Lomogin.

DRUG INTERACTIONS

There is no evidence that Lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising 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 antiepileptic drugs have been reported, controlled studies have shown no evidence that Lamotrigine affects the plasma concentrations of concomitant antiepileptic drugs. Evidence from in-vitro studies indicates that Lamotrigine does not displace other antiepileptic drugs from protein binding sites. Lamotrigine did not affect plasma concentrations of ethinyloestradiol and levonorgestrel following the administration of the oral contraceptive pill. However as with the introduction of other chronic therapy in patients taking oral contraceptives, any change in the menstrual bleeding pattern should be reported to the patient's physician. Antiepileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone), which induce hepatic drug-metabolising enzymes, enhance the metabolism of Lamotrigine. Valproate, which competes with Lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of Lamotrigine. There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of Lamotrigines. These events usually resolve when the dose of carbamazepine is reduced.

PREGNANCY AND LACTATION

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

TERATOGENICITY: Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.
However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.

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

LACTATION: 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 experiences were reported.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As there is individual variation in response to all antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

ADVERSE REACTIONS

Adverse experiences reported during Lamotrigine monotherapy trials include headache, tiredness, rash, nausea, dizziness, drowsiness and insomnia. Skin rashes occurred 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 Johnson 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 rare cases of associated death. The overall risk of rash appears to be strongly associated with:

- High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy.
- Concomitant use of valproate, which increases the mean half-life of lamotrigine nearly two fold.

Rash has also been reported as part of a 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 (DIC) and multiorgan failure. If such signs and symptoms are present the patient should be evaluated immediately and Lomogin discontinued if an alternative aetiology cannot be established. Other adverse experiences reported when lamotrigine is added-on to standard antiepileptic drug regimens have included diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, headache, unsteadiness, tiredness, gastrointestinal disturbance (including vomiting), irritability/aggression, tremor, confusion and haematological abnormalities (including leucopenia and thrombocytopenia).

OVER-DOSAGE

SYMPTOMS AND SIGNS: Ingestion of between 1.35 and 4g lamotrigine has been reported in a few patients. 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 5g 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 5.6g 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 over-dosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

MODE OF ACTION

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

PHARMACOKINETICS

Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 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 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentration vary very little. 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. The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of Lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy subjects is 24 to 35 hours; UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of Lamotrigine. Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that Lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between Lamotrigine and drugs metabolized by cytochrome P450 enzymes are unlikely to occur. The half-life of Lamotrigine is greatly affected by concomitant medication. The 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 coadministered with sodium valproate alone.
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.
To date there have been no specific studies of Lamotrigine Pharmacokinetics in elderly patients with epilepsy. However no dose adjustment is required for the elderly. There is no experience of treatment with Lamotrigine of patients with renal failure. Pharmacokinetics studies using single dose in subjects with renal failure indicates that Lamotrigine Pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight fold due to reduced renal clearance.

MUTAGENICITY

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

CARCINOGENICITY

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

INSTRUCTIONS

Store below 30°C. Protect from heat, light & moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

Lomogin 25mg tablets: Available in blister pack of 3x10's
Lomogin 50mg tablets: Available in blister pack of 3x10's
Lomogin 100mg tablets: Available in blister pack of 3x10's

لوموجن ٹیبلیٹس

(لیمو ٹرائی جن) یو ایس پی

ہدایات: **30°** سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
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