25mg

Limgit®

(Lamotrigine)

30 Tablets

Amarant

Limgit®

(Lamotrigine 25mg, 50mg & 100mg Tablets)

لیمگٹ

(لیموٹرا جین ۲۵ ملی گرام، ۵۰ ملی گرام اور ۱۰۰ ملی گرام ٹیبلٹس)

COMPOSITION

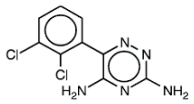
Limgit 25mg Tablet
Each film coated tablet contains:
Lamotrigine 25mg

Limgit 50mg Tablet
Each film coated tablet contains:
Lamotrigine 50mg

Limgit 100mg Tablet
Each film coated tablet contains:
Lamotrigine 100mg

DESCRIPTION

Lamotrigine, an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Lamotrigine's chemical name is 3,5-diamino-6-(2,3- dichlorophenyl) -as-triazine, its molecular formula is $C_9H_7N_5C_{l_2}$ and its molecular weight is 256.09. The structural formula is:



CLINICAL PHARMACOLOGY

Mechanism Of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. However, In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids. The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

Pharmacokinetics

Absorption

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 is 1.4 to 4.8 hours following drug administration.

Protein Binding

Data from in vitro studies indicate that lamotrigine is approximately 55% bound to human plasma proteins.

Metabolism

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate.

Special Populations: Elderly

Clearance was 0.3 to 0.5 mL/minute/kg.

Special Populations: Gender

Mean trough concentrations were 24% to 45% higher in women than men.

Special Populations: Race

Oral clearance was 25% lower in nonwhite patients than in white patients.

Excretion

Urine (94%, ~90% as glucuronide conjugates and ~10% unchanged); feces (2%).

INDICATIONS

Epilepsy

Adjunctive Therapy

Lamotrigine is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older:
- Partial-onset seizures.
- Primary generalized tonic-clonic (PGTC) seizures.
- Generalized seizures of Lennox-Gastaut syndrome.

Monotherapy

Lamotrigine is indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).

Bipolar Disorder

Lamotrigine is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults (aged 18 years and older) treated for acute mood episodes with standard therapy.

DOSAGE

General Dosing Considerations

Rash

There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) co-administration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. It is recommended that lamotrigine not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly outweigh the risks.

Lamotrigine Added to Drugs Known to Induce or Inhibit Glucuronidation

Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine may require adjustment based on clinical response.

Target Plasma Levels for Patients With Epilepsy or Bipolar Disorder

A therapeutic 88 plasma concentration range has not been established for lamotrigine. Dosing of Lamotrigine should be based on therapeutic response.

Women Taking Estrogen-Containing Oral Contraceptives

Starting lamotrigine in Women Taking Estrogen - Containing Oral Contraceptives Oral contraceptives have been shown to increase the clearance of lamotrigine, no adjustments to the recommended dose-escalation guidelines for Lamotrigine should be necessary solely based on the use of estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of lamotrigine in Women Taking Estrogen-Containing Oral Contraceptives

(1) *Taking Estrogen-Containing Oral Contraceptives:* In women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation, the maintenance dose of lamotrigine will in most cases need to be increased by as much as 2-fold over the recommended target maintenance dose to maintain a consistent lamotrigine plasma level.

(2) *Starting Estrogen-Containing Oral Contraceptives:* In women taking a stable dose of lamotrigine and not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation., the maintenance dose will in most cases need to be increased by as much as 2-fold to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100mg/day every week.

(3) *Stopping Estrogen-Containing Oral Contraceptives:* In women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation, the maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of lamotrigine should not exceed 25% of the total daily dose per week over a 2-week period.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy

It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine in the presence of progestogens alone will likely not be needed.

Epilepsy – Adjunctive Therapy

Escalation Regimen for lamotrigine in Patients Older than 12 Years with Epilepsy

Weeks 1 and 2:
- In Patients TAKING Valproate: 25mg every other day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 25mg every day.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 50mg/day.

Weeks 3 and 4:
- In Patients TAKING Valproate: 25mg every day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 50mg/ day.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 100mg/day (in 2 divided doses).

Week 5 onward to maintenance
- In Patients TAKING Valproate: Increase by 25 to 50mg/day every 1 to 2 weeks.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate: Increase by 50mg/day every 1 to 2 weeks.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: Increase by 100mg/day every 1 to 2 weeks.

Usual maintenance dose
- In Patients TAKING Valproate: 100 to 200mg/day with valproate alone 100 to 400mg/day with valproate and other drugs that induce glucuronidation (in 1 or 2 divided doses).
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 225 to 375mg/day (in 2 divided doses).
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 300 to 500mg/day (in 2 divided doses).

Escalation Regimen for Lamotrigine in Patients Aged 2 to 12 Years with Epilepsy

Weeks 1 and 2:
- In Patients TAKING Valproate: 0.15mg/kg/day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 0.3mg/kg/day in 1 or 2 divided doses.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 0.6mg/kg/day in 2 - divided dose.

Weeks 3 and 4:
- In Patients TAKING Valproate: 0.3mg/kg/day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 0.6mg/kg/day in 2 divided doses.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 1.2mg/kg/day in 2 divided doses.

Week 5 onward to maintenance
- In Patients TAKING Valproate: The dose should be increased every 1 to 2 weeks as follows: calculate 0.3mg/kg/day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: The dose should be increased every 1 to 2 weeks as follows: calculate 0.6mg/kg/day.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: The dose should be increased every 1 to 2 weeks as follows: calculate 1.2mg/kg/day.

Usual maintenance dose
- In Patients TAKING Valproate: 1 to 5mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses) 1 to 3mg/kg/day with valproate alone.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 4.5 to 7.5mg/kg/day (maximum 300mg/day in 2 divided doses).
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 5 to 15mg/kg/day (maximum 400mg/day in 2 divided doses).

Maintenance dose in patients less than 30 kg
- In Patients TAKING Valproate: May need to be increased by as much as 50%, based on clinical response.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: May need to be increased by as much as 50%, based on clinical response.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: May need to be increased by as much as 50%, based on clinical response.

Bipolar Disorder

The goal of maintenance treatment with lamotrigine is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

Adults

The target dose of Lamotrigine is 200mg/day (100mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400mg /day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitor lopinavir/ritonavir that increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400mg/day as monotherapy were evaluated; however, no additional benefit was seen at 400mg/day compared with 200mg /day. Accordingly, doses above 200mg/day are not recommended.

Escalation Regimen for Lamotrigine in Adults with Bipolar Disorder

Weeks 1 and 2:
- In Patients TAKING Valproate: 25mg every other day.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate: 25mg daily.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 50mg daily.

Weeks 3 and 4:
- In Patients TAKING Valproate: 25mg daily.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 50mg daily.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 100mg daily, in divided doses.

Week 5
- In Patients TAKING Valproate: 50mg daily.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 100mg daily.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: 200mg daily, in divided doses.

Week 6
- In Patients TAKING Valproate: 100mg daily.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 200mg daily.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproatea: 300mg daily, in divided doses.

Week 7
- In Patients TAKING Valproate: 100mg daily.
- In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate: 200mg daily.
- In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone and NOT TAKING Valproate: Upto 400mg daily, in divided doses.

USE IN SPECIFIC POPULATION

Pregnancy

As with other AEDs, 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. Lamotrigine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers 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.

Hepatic Impairment

Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 subjects with mild, moderate, and severe liver impairment.

Geriatric Use

Clinical trials of lamotrigine for epilepsy and bipolar disorder did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients or exhibit a different safety profile than that of younger patients.

Renal Impairment

Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine.

SIDE EFFECTS
- Serious skin rashes
- Suicidal behavior and ideation
- Withdrawal seizures
- Sudden unexplained death in epilepsy
- Multiorgan hypersensitivity reactions and organ failure
- Blood dyscrasias
- Aseptic meningitis
- Status epilepticus

DRUG INTERACTIONS

Estrogen-containing Oral contraceptive preparations containing 30mcg ethinylestradiol and 150mcg levonorgestrel

Concomitant administration of estrogen containing oral contraceptives decreased lamotrigine concentrations approximately 50%.

Carbamazepine and carbamazepine epoxide

Addition of carbamazepine decreases lamotrigine concentration approximately 40%. But may increase carbamazepine epoxide levels.

Lopinavir/Ritonavir

Concomitant administration of Lopinavir and Ritonavir decreased lamotrigine concentration approximately 50%.

Atazanavir/Ritonavir

Concomitant administration of Azatanavir and Ritonavir decreased lamotrigine AUC approximately 32%.

Phenobarbital/Primidone/Phenytoin

Concomitant administration of these drugs decreased lamotrigine concentration approximately 40%.

Rifampin

Concomitant administration of Rifampin decreased lamotrigine AUC approximately 40%.

Valproate

Administartion of valproate with lamotrigine , increased lamotrigine concentrations slightly more than 2-fold. There are conflicting study results regarding effect of lamotrigine on valproate concentrations: 1) a mean 25% decrease in valproate concentrations in healthy volunteers, 2) no change in valproate concentrations in controlled clinical trials in patients with epilepsy.

CONTRAINDICATIONS

Lamotrigine is contraindicated in patients who have demonstrated hypersensitivity (e.g., rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its ingredients.

WARNINGS AND PRECAUTIONS

Pediatric Population

The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in a prospectively followed cohort of pediatric patients (aged 2 to 16 years) with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983). There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients.

Adult Population

Serious rash associated with hospitalization and discontinuation of lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who received lamotrigine in premarketing clinical trials of epilepsy.

Patients with History of Allergy or Rash to Other Antiepileptic Drugs

The risk of non-serious rash may be increased when the recommended initial dose and/or the rate of dose escalation for lamotrigine is exceeded and in patients with a history of allergy or rash to other AEDs.

Multiorgan Hypersensitivity Reactions And Organ Failure

Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred with lamotrigine.

Blood Dyscrasias

There have been reports of blood dyscrasias that may or may not be associated with multiorgan hypersensitivity.

Suicidal Behavior and Ideation

AEDs, including lamotrigine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.

OVERDOSE

Human Overdose Experience

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

Management Of Overdose

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.

STORAGE

Store below 30°C.
Protect from light, heat and moisture.
Keep out of the reach of Children.

PRESENTATION

Limgit (Lamotrigine) 25mg Tablet: Pack of 30's in Alu-Alu blister.
Limgit (Lamotrigine) 50mg Tablet: Pack of 30's in Alu-Alu blister.
Limgit (Lamotrigine) 100mg Tablet: Pack of 30's in Alu-Alu blister.

خوراک اور ہدایات:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو **30** درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، گرمی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

(R002)

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