LAMOTRIX ®
(Lamotrigine)

COMPOSITION: LAMOTRIX® tablets contain 25, 50, 100 and 200mg of lamotrigine.

PHARMACEUTICAL FORM:
LAMOTRIX® 25mg tablets are beige coloured, round, flat, marked MC at one side, with diameter 6mm.
LAMOTRIX® 50mg tablets are beige coloured, round, flat and have a break-line, with diameter 8mm.
LAMOTRIX® 100mg tablets are beige coloured, round, flat and have a break-line, with diameter 9.5mm.
LAMOTRIX® 200mg tablets are beige coloured, round, flat and have a break-line, with diameter 12.7mm.

PHARMACOLOGY:
Pharmacokinetic properties: Lamotrigine is readily absorbed from the gut with no significant first pass metabolism. Peak plasma concentration occurs in about 2.5 hours. The presence of food would delay the time to reach maximum concentration but the extent of absorption is not affected.
The pharmacokinetics are linear up to doses of 450mg. There is considerable inter-individual variation in steady state maximum concentrations but within and individual concentrations vary very little.
About 55% of lamotrigine is protein bind. Displacement from plasma protein is highly unlikely to lead to toxicity. The volume of distribution (Vd) is 0.92 to 1.22 l/kg.
When given as monotherapy, lamotrigine induces its own metabolism to a modest extend depending on dose. Lamotrigine does not affect the pharmacokinetics of other AEDs or drugs that metabolised by cytochrome P450 enzymes.
The mean steady state of clearance in healthy adults is 39 ± 14ml/min and it is independent of the dose. Lamotrigine is metabolised to 2-N-glucuronide conjugate (inactive) which is the major metabolite, representing 70% of total metabolites. Also, to 5-N-glucuronide conjugate (inactive) and to 2-N-methyl metabolite (inactive). The enzymes responsible for metabolism of lamotrigine are the up-glucuronyl transferases. Less than 10% is excreted unchanged in urine and 2% in faeces. The mean elimination half-life is 24 to 35 hours.
In adults, the co-administration of lamotrigine and enzyme-inducing drugs such as carbamazepine and phenytoin reduced the half-life of lamotrigine to approximately 14 hours. The co-administration of lamotrigine and sodium valproate alone increased the half-life to a mean of approximately 70 hours.
In children the half-life is shorter than in adults with a mean value of approximately 7 hours when given with enzyme inducing drugs such as carbamazepine and phenytoin. The half-life increases to 45-55 hours when co-administered with sodium valproate alone. The clearance rate is higher in children (aged 12 and under) than in adults. The highest values are reported in children less than 5 years.
Lamotrigine therapy in patients with renal failure has not been extensively investigated. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

Pharmacodynamic properties: Lamotrigine is an antiepileptic drug of the phenyltriazine class. The exact mechanism of action of lamotrigine has not been fully elucidated. It appears to act at voltage-sensitive sodium channels to stabilise neuronal membranes. It inhibits neurotransmitter release, namely glutamate and it inhibits glutamate-evoked bursts of action potential. Glutamate is an amino acid excitatory neurotransmitter who plays a key role in the generation of epileptic seizures.

INDICATIONS:
Lamotrigine is indicated as an adjunctive therapy in treatment of partial seizures and generalised tonic-clonic seizures. As a supplementary (add-on) treatment against seizure in connection with Lennox-Gastaut Syndrome in patient more than 3 years of age.

RECOMMENDED DOSAGE AND ROUTE OF ADMINISTRATION:
The tablets should be swallowed whole with a little water.
The therapeutic maintenance dose for children has to be monitored according with the child's weight and to be adjusted if any weight changes occur. If the doses calculated for children, according to body weight, do not equate to whole tablets, the dose administered should be equal to the lower number of the whole tablets.

Dosage in add-on therapy: *Adults and children over 12 years: In patients taking valproate with/without any other anti-epileptic drug (AED) the initial lamotrigine 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 patients taking enzyme inducing AEDs with/without other AEDs (except valproate) the initial lamotrigine 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 200-400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In case patients are receiving AEDs that the pharmacokinetic interactions with lamotrigine are not known, the dose escalation should be the one recommended for lamotrigine with concurrent valproate. Thereafter, the dose should be increased until optimal response is achieved.

The following table (Table 2) shows the recommended dose escalation of lamotrigine for adults and children over 12 years on combined drug therapy.

Table 2:

Concomitant medication	Weeks 1-2	Weeks 3-4	Usual maintenance dose
Valproate with/without any other AEDS	12.5mg (given as 25mg on 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[*1] 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

*[*1] For example phenytoin, carbamazepine, phenobarbitone and primidone*

***Note**: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is not known, the dose escalation should be the one recommended for lamotrigine with concurrent valproate administration. Thereafter, the dose should be increase until optimal response is achieved.*

The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see Warnings and precautions).

Children aged 2 to 12 years: In patients taking valproate with/without any other anti-epileptic drug (AED) the initial lamotrigine dose is 0.2 mg/kg body-weight/day given once a day for two weeks, followed by 0.5 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.5-1 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses.

In patients taking enzyme inducing AEDs with/without other AEDs (except valproate) the initial lamotrigine dose is 2 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 5mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of 2-3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses.

In case patients are receiving AEDs that the pharmacokinetic interactions with optimal response is achieved.

The following table (Table 3) shows the recommended dose escalation of lamotrigine for children aged 2-12 years on combined drug therapy. (Total daily dosage in mg/kg bodyweight/day).

Table 3:

Concomitant medication	Weeks 1-2	Weeks 3-4	Usual maintenance dose
Valproate with/without any other AEDS	0.2 mg/kg[*2] (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 0.5-1 mg/kg every 1-2 weeks
Enzyme inducing AEDs[*1] 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 2-3 mg/kg every 1-2 weeks

*[*1] For example phenytoin, carbamazepine, phenobarbitone and primidone*

*[*2] If the calculated daily dose is 2.5-5 mg, then 5mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 2.5mg, then lamotrigine should not be administered.*

Note: *In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is not known, the dose escalation should be the one recommended for lamotrigine with concurrent valproate administration. Thereafter, the dose should be increase until optimal response is achieved.*

The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see Special warnings and precautions).

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 data on the use of lamotrigine in children aged less than 2 years.*

Use in the elderly: *There is limited data on the use of lamotrigine. Even though, there is no current evidence to suggest that the elderly patients would react any different from the young ones, caution is strongly advised.*

CONTRAINDICATIONS:
Lamotrigine is contra-indicated in patients:
- with known hypersensitivity to lamotrigine.
- with significant impairment of hepatic function.

WARNINGS & PRECAUTIONS:
Potential for an increase in risk of suicidal thoughts or behaviors.

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/ Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lympha-denopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established.

Lamotrigine therapy may evoke adverse skin reactions, usually during the first 2 months of treatment. The majority of them are mild and self-limiting. Rarely, serious and potentially life-threatening rash may appear (including Stevens Johnson syndrome and toxic epidermal necrolysis) (see *Adverse Reactions*).

For adults and children over 12 years old the incidence of serious skin rashes is 1 in 1000. That risk appears to be higher in children less than 12 years old (1 in 300 to 1 in 100).

The presence of rash in children may be mistaken considered as an infection. The doctor should always consider the possibility of an adverse skin reaction in children that develop rash and fever during the first 2 months of treatment.

The risk of the appearance of rash is increased when the initially administered dose of lamotrigine is higher than the one recommended. Also, when it is administered concomitantly with valproate, since lamotrigine's mean half-life is increased up to two hours.

Patients who develop rashes should discontinue lamotrigine unless the rash is clearly not drug related. It is not possible to predict reliably which rashes will prove to be life threatening, thus lamotrigine should be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment, though, may not prevent a rash from becoming life threatening or permanently disabling or disfiguring.

Rash may be part of hypersensitivity syndrome, associated with various symptoms, such as fever, lymphadenopathy, facial oedema, and haematological or hepatic abnormalities. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to Disseminated Intravascular Coagulation (DIC) and multiorgan failure. It is important to note that early signs of hypersensitivity (e.g., fever, and lymphadenopathy) may be present even though a rash is not evident. The doctor should instruct the patient to recognise the first signs of hypersensitivity, so as to ask immediately for proper medical assistance. If such symptoms are present, the patient should be evaluated immediately. *If no alternative aetiology for the symptoms can be established lamotrigine should be discontinued*

Similarly with other anti-epileptic drugs, lamotrigine should not be abruptly discontinued because it may provoke rebound seizures. Unless safety concerns require an immediate withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

In cases where either concomitant antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or antiepileptic drugs are added-on to lamotrigine monotherapy, it is important to consider the relevant effects it may have on the pharmacokinetics of lamotrigine.

When lamotrigine was used as an adjunctive therapy, there have been rarely deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events has not been established.

Lamotrigine, being a weak inhibitor of dihydrofolate reductase might interfere with the folate metabolism. 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 for up to 1 year or red blood cell folate concentrations for up to 5 years.

In patients with end-stage renal failure an accumulation of the glucoronide metabolite is expected. Although the pharmacokinetic behaviour of the drug remains the same after a single-dose administration caution should be exercised in such patients during long-term treatment.

Brugada-type ECG
A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using Lamotrix in patients with Brugada syndrome.

INTERACTIONS WITH OTHER MEDICAMENTS:
Antiepileptic agents such as phenytoin, carbamazepine, phenobarbitone and primidone enhance the metabolism of lamotrigine. Dosage requirements of lamotrigine may be increased.

Sodium valproate competes with lamotrigine for hepatic drug-metabolism enzymes and in effect it reduces the metabolism of lamotrigine.

Lamotrigine does not seem to cause clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. Lamotrigine may induce its own metabolism that is modest and unlikely to induce any clinically significant effect.

Lamotrigine does not affect the plasma concentration of co-administered antiepileptic agents. In vitro studies have shown that lamotrigine does not displace other antiepileptic agents from protein binding sites.

Administration of lamotrigine in patients already receiving carbamazepine has given rise to events such as headache, nausea, blurred vision, dizziness, diplopia and ataxia. These events are transient upon reduction of carbamazepine dose.

Although there is no evidence that lamotrigine alters plasma levels of ethinyloestradiol and levonorgestrel, patients taking oral contraceptives should report to their doctor any changes in their menstrual bleeding pattern.

PREGNANCY AND LACTATION:
Pregnancy category: C.
The effect of lamotrigine during pregnancy in humans is unknown. Thus, lamotrigine should not be given to pregnant patients unless the potential benefit outweighs the possible risks to the foetus.
Lamotrigine is excreted into human milk in concentrations usually of 40-45% of the plasma concentration. Even though, no adverse reactions have been reported in the infant, breast-feeding is not recommended during lamotrigine therapy.

ADVERSE REACTIONS:
Lamotrigine monotherapy might cause headache, tiredness, rash, nausea, dizziness, drowsiness and insomnia.

Skin rashes occur in 5% of patients taking lamotrigine and lead to withdrawal of treatment in about 2% of patients. The rash, usually maculopapular in appearance, generally appears within 2 months of initiation of 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. The majority recovers on drug withdrawal. Some patients, though, experience irreversible scarring and there have been rare cases of associated death.

The approximate incidence of serious skin rashes in adults and children over the age of 12 is 1 in 1000. The risk is higher in children under the age of 12 (1 to 300 to 1 to 100).

The risk of rash increases when lamotrigine is co-administered with valproic acid (VPA) and when the recommended initial dose of lamotrigine and the recommended dose escalation for lamotrigine are exceeded.

Patients who develop rashes should discontinue lamotrigine. It is not possible to predict reliably which rashes will prove to be life threatening, thus lamotrigine should be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment, though, may not prevent a rash from becoming life threatening or permanently disabling or disfiguring. (see *Warnings and Precautions*).

Hypersensitivity reactions, some fatal or life threatening, have also occurred. Some of these reactions have associated with variable systemic symptoms including fever, lymphadenopathy, facial oedema, and haematological and hepatologic abnormalities. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to Disseminated Intravascular Coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, and lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Lamotrigine should be discontinued if an alternative aetiology for the signs or symptoms cannot be established. (see *Warnings and Precautions*).

Adverse reactions reported when lamotrigine is added-on to standard antiepileptic drug regimes may include diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, headache, unsteadiness, tiredness, gastrointestinal disturbance (including vomiting), irritability/aggression, tremor, agitation, confusion and haematological abnormalities (including neutropenia, leucopenia and thrombocytopenia).

Post-marketing
Blood and lymphatic system disorders
Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINERIES:
In some individuals lamotrigine therapy may cause neurological type adverse reactions (such as dizziness, somnolence). Therefor at the beginning of the treatment and until the response to lamotrigine has been clarified patients should be advised not to drive or to operate machinery.

SYMPTOMS & TREATMENT OF OVERDOSE:
Reported cases of lamotrigine overdose involve ingestion of 1.35 and 4g lamotrigine. The signs and symptoms of lamotrigine overdosed include nystagmus, ataxia, dizziness, somnolence, headache and vomiting.
Also, a case of a patient who ingested a dose between 4 and 5g lamotrigine has been reported. He was admitted to hospital in coma lasting 8-12 hours. He finally recovered over the next 2 to 3 days. Another patient ingested 5.6g of lamotrigine. He was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours
In case of overdosage, the patient should be admitted to hospital and receive supportive treatment. If indicated gastric lavage should be performed.

PACKAGING & PACK SIZES: PVC/Al blisters of 10 tablets.
LAMOTRIX® Tablets 25mg: Boxes of 30 tablets
LAMOTRIX® Tablets 50mg: Boxes of 30 tablets
LAMOTRIX® Tablets 100mg: Boxes of 30 tablets
LAMOTRIX® Tablets 200mg: Boxes of 30 tablets

STORAGE CONDITIONS: Store below 30°C in the original package

SHELF LIFE: 36 months

NAME & ADDRESS OF MANUFACTURER: MEDOCHEMIE (FAR EAST) LTD., (Oral Facility), No.40, VSIP II Street 6, Vietnam-Singapore Industrial Park II, Binh Duong Industry-Service-Urban Complex, Hoa Phu ward, Thu Dau Mot city, Binh Duong province, Vietnam

NAME & ADDRESS OF PRODUCT REGISTRATION HOLDER: KOMEDIC SDN BHD, 4 Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya, Selangor DE.

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