SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

LAMITOR–25 (tablet)

LAMITOR–50 (tablet)

LAMITOR–100 (tablet)

LAMITOR–200 (tablet)

COMPOSITION

LAMITOR–25: Each tablet contains lamotrigine 25 mg

LAMITOR–50: Each tablet contains lamotrigine 50 mg

LAMITOR–100: Each tablet contains lamotrigine 100 mg

LAMITOR–200: Each tablet contains lamotrigine 200 mg

Contains sugar (lactose monohydrate)

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Antiepileptics

PHARMACOLOGICAL ACTION

Lamotrigine blocks voltage-sensitive sodium channels, thereby stabilising neuronal membranes and inhibiting neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a key role in the generation of epileptic seizures.

Pharmacokinetics

Lamotrigine is rapidly and completely absorbed from the gut. The absorption is unaffected by food. The time to peak concentration is 1,4 to 4,8 hours. The mean elimination half-life is 25 ± 10 hours and the pharmacokinetic profile is linear up to 450 mg, the highest single dose tested. The half-life of lamotrigine is affected by concomitant use of enzyme-inducing drugs such as phenytoin, carbamazepine, phenobarbital or primidone with a mean value of approximately 14 hours.

The half-life of lamotrigine increases to approximately 59 hours when co-administered with valproic acid alone (see **DOSAGE AND DIRECTIONS FOR USE**). Following multiple administration of lamotrigine (150 mg twice daily) there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. Lamotrigine is moderately (55 %) bound to plasma proteins.

Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children under 5 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.

INDICATIONS

Adults and children over 12 years

LAMITOR is indicated as monotherapy or add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures.

Children 2 to 12 years

LAMITOR is indicated as add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures not satisfactorily controlled with other antiepileptic medicines. Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Lennox-Gastaut Syndrome

LAMITOR is indicated as add-on treatment for seizures associated with Lennox-Gastaut Syndrome.

CONTRAINDICATIONS

LAMITOR is contraindicated in the following circumstances:

- Individuals with known hypersensitivity to lamotrigine.
- The safety of **LAMITOR** in pregnancy and lactation has not been established.
- Renal and hepatic function impairment. Hepatic metabolism followed by renal excretion is the principal route of elimination of lamotrigine and until more information is available, the use of **LAMITOR** in patients with impairment of hepatic or renal function is contraindicated.
- Patients over the age of 65 years.

WARNINGS

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 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 AND SPECIAL PRECAUTIONS**). Isolated cases have been reported after prolonged treatment (6 months).

The estimated incidence of serious skin rashes in adults is 1 in 1 000. The risk is higher in children than in adults. Some children may require hospitalisation because of the seriousness of skin rashes.

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.

No evidence was shown that **LAMITOR** affects the plasma concentration of concomitant antiepileptic drugs. **LAMITOR** does not displace other antiepileptic drugs from protein binding sites.

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 does not seem to 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.

PREGNANCY AND LACTATION

The safety of **LAMITOR** in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

It is important to adhere to the recommended dosages especially in combination therapy with valproate where one-tenth of the normal dose is used.

Do not exceed the maximum dosage (see **WARNINGS**). To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed if necessary. 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.

Dosage in monotherapy:

Adults and children over 12 years of age

Initial dose in monotherapy: 25 mg once daily for two weeks, followed by 50 mg once daily for two weeks. The dosage may be increased by a maximum of 50 – 100 mg every 1 to 2 weeks until the optimal response is achieved.

Maintenance dose in monotherapy: The usual dose to achieve optimal response is 100 – 200 mg per day given in one dose or two divided doses. Some patients have required 500 mg/day of **LAMITOR** to achieve the desired response.

Adults and Children over 12 years (total daily dose)

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.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **WARNINGS**).

Dosage in add-on therapy:

Adults and children over 12 years of age

The initial LAMITOR dose in those patients not taking sodium valproate: The initial dose is 50 mg once a day for two weeks, then 100 mg a day, divided into two doses, for two weeks. The dosage may be increased by a maximum of 100 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 200 – 400 mg/day given in two divided doses.

In those patients taking sodium valproate: The initial dose is 25 mg once every other day for two weeks, then 25 mg once a day for two weeks. The dosage may be increased by a maximum of 25 – 50 mg a day every 1 or 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 patients taking antiepileptic drugs where the pharmacokinetic interaction with **LAMITOR** is currently not known, the dose escalation as recommended for **LAMITOR** with concurrent valproate should be used. Thereafter, the dose should be increased until the optimal response is achieved.

Adults and Children over 12 years (total daily dose)

	Weeks 1 & 2	**Weeks 3 & 4**	**Maintenance Dose**
Patients not taking sodium valproate	50 mg (once a day)	100 mg (two divided doses)	200 – 400 mg (two divided doses). To achieve maintenance, doses may be increased by 100 mg every 1 – 2 weeks.
Patients taking sodium valproate	25 mg (on alternative days)	25 mg (once a day)	100 – 200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 25 - 50 mg every 1 – 2 weeks.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **WARNINGS**).

Children aged 2 to 12 years

The initial LAMITOR dose in those children not taking sodium valproate: The initial dose is 0,6 mg/kg body-weight daily given in two divided doses for two weeks, followed by 1,2 mg/kg daily in 2 divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1,2 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 5 – 15 mg/kg/day given in two divided doses. A maximum daily dose of 400 mg must not be exceeded.

In those children taking sodium valproate: The initial dose of 0,15 mg/kg once daily for two weeks, followed by 0,3 mg/kg once daily for two weeks. Thereafter the dose is increased by a maximum of 0,3 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 1 – 5 mg/kg, which may be given once a day or in two divided doses. A maximum daily dose of 200 mg must not be exceeded.

In patients taking antiepileptic drugs where the pharmacokinetic interaction with **LAMITOR** is currently not known, the dose escalation as recommended for **LAMITOR** with concurrent valproate should be used. Thereafter, the dose should be increased until the optimal response is achieved.

Children aged 2 to 12 years (total daily dose)

	Weeks 1 & 2	**Weeks 3 & 4**	**Maintenance Dose**
Patients not taking sodium valproate	0,6 mg/kg (two divided doses)	1,2 mg/kg (two divided doses)	5 – 15 mg/kg (two divided doses) or maximum of 400 mg daily. To achieve maintenance, doses may be increased by 1,2 mg/kg every 1 – 2 weeks.
Patients taking sodium valproate	0,15 mg/kg (once a day)	0,3 mg/kg (once a day)	1 – 5 mg/kg (once a day or in two divided doses). or maximum of 200 mg

			daily. To achieve maintenance, doses may be increased by 0,3 mg every 1 – 2 weeks.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **WARNINGS**).

Note: If the calculated daily dose is 2,5 – 5 mg, then 5 mg **LAMITOR** may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 2,5 mg, then **LAMITOR** should not be administered. Patients aged 2 – 6 years may require a maintenance dose at the higher end of the recommended range.

Dosage in seizures associated with Lennox-Gastaut Syndrome:

The dosing guidelines outlined above for both adults and children aged 2 – 12 years apply for the treatment of seizures associated with Lennox-Gastaut Syndrome.

Children aged less than 2 years

There is insufficient information on the use of **LAMITOR** in children aged less than two years.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

SIDE-EFFECTS

Very common (> 1/10), Common (> 1/100 and ≤ 1/10), *Uncommon (> 1/1000 and ≤ 1/100), Rare (> 1/10 000 and ≤ 1/1000), Very rare (≤ 1/10 000)*

Blood and lymphatic system disorders

Very rare: Blood dyscrasias including anaemia, eosinophilia, leucopenia or thrombocytopenia

Immune system disorder

Very rare: Hypersensitivity syndrome. Symptoms such as fever, malaise, influenza-like symptoms, drowsiness, lymphadenopathy, facial oedema and rarely, hepatic dysfunction, leucopenia and thrombocytopenia have been reported in conjunction with rashes as part of a hypersensitivity syndrome (see **WARNINGS**).

Skin and subcutaneous tissue

disorders

Very common: Skin rash

Rare: Stevens-Johnson Syndrome, photosensitivity

Very rare: Toxic epidermal necrolysis

Severe skin rashes, including Stevens-Johnson Syndrome have been reported, especially in children. The skin rash usually occurs within 8 weeks of starting **LAMITOR** and resolves on withdrawal of **LAMITOR** (see **WARNINGS)**.

Nervous system disorders

Very common: Headache

Common: Tiredness, insomnia, drowsiness, dizziness, anxiety, confusion, depression, irritability, nystagmus, tremor and ataxia

Uncommon: Increased seizures, coordination abnormalities

Eye disorders

Very common: Vision abnormalities, including blurred vision, diplopia

Respiratory, thoracic and mediastinal disorders

Rare: Angio-oedema (trouble in breathing, swelling of face, mouth, hands or feet)

Gastrointestinal disorders

Common: Nausea and vomiting

PRECAUTIONS

LAMITOR inhibits dihydrofolate reductase and should be used with caution with other folate antagonists.

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.

IDENTIFICATION

LAMITOR–25: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side

LAMITOR–50: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side

LAMITOR–100: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side

LAMITOR–200: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side

PRESENTATION

LAMITOR–25: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton

LAMITOR–50: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton

LAMITOR–100: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton

LAMITOR–200: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton

STORAGE INSTRUCTIONS

Store at or below 25 ºC in a dry place

Keep tablets in the original blister packs until a dose is to be taken.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

LAMITOR–25: 37/2.5/0051

LAMITOR-50: 37/2.5/0052

LAMITOR-100: 37/2.5/0053

LAMITOR-200: 41/2.5/0375

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Limited

The Place

1 Sandton Drive

Sandton

2196

DATE OF PUBLICATION OF THE PACKAGE INSERT

December 2008