LAMICTIN® RANGE

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

LAMICTIN® 25, **50**, **100** and **200** Tablets

LAMICTIN® P2, **P5**, **P25**, **P50**, **P100** and **P200** Dispersible Tablets

COMPOSITION:

Each LAMICTIN 25 tablet contains: 25 mg lamotrigine

Contains lactose monohydrate (24,7 mg/tablet)

Each LAMICTIN 50 tablet contains: 50 mg lamotrigine

Contains lactose monohydrate (49,4 mg/tablet)

Each LAMICTIN 100 tablet contains: 100 mg lamotrigine

Contains lactose monohydrate (98,8 mg/tablet)

Each LAMICTIN 200 tablet contains: 200 mg lamotrigine

Contains lactose monohydrate (114,7 mg/tablet)

Excipients: The other ingredients of LAMICTIN tablets are lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycollate, iron oxide yellow (E172) and magnesium stearate.

Each LAMICTIN P2 dispersible tablet contains: 2 mg lamotrigine

Each LAMICTIN P5 dispersible tablet contains: 5 mg lamotrigine

Each LAMICTIN P25 dispersible tablet contains: 25 mg lamotrigine

Each LAMICTIN P50 dispersible tablet contains: 50 mg lamotrigine

Each LAMICTIN P100 dispersible tablet contains: 100 mg lamotrigine

Each LAMICTIN P200 dispersible tablet contains: 200 mg lamotrigine

Excipients: The other ingredients of LAMICTIN dispersible tablets are calcium carbonate, low substituted hydroxypropyl cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone, saccharin sodium, blackcurrant flavour and magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

The results of pharmacological studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilise neuronal membranes and inhibit neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a key role in the generation of epileptic seizures.

Clinical efficacy in the prevention of depressive episodes in patients with bipolar disorder: Two pivotal studies have demonstrated efficacy in the prevention of depressive episodes in patients with bipolar I disorder.

One was a multi-centre, double-blind, double-dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200, 400 mg/day), lithium (serum levels of 0,8 to 1,1 mEq/ℓ)

or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was 'Time to Intervention for a Mood Episode (TIME)', where the interventions were either additional pharmacotherapy or ECT. This endpoint was analyzed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0,003 to 0,029. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine patients had longer times to first depressive episode than placebo patients (p = 0,047) and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

Another study was a multi-centre, double-blind, double-dummy, placebo and lithium-controlled, randomised, flexible dose evaluation of lamotrigine in the long-term prevention of relapse and recurrence of manic and/or depression in patients with bipolar I disorder who had recently or were currently experiencing a manic or hypomanic episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of three treatment groups: lamotrigine (100 to 400 mg/day), lithium (serum levels of 0,8 to 1,1 mEq/ℓ) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

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patients (p = 0,015) and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on lamotrigine therapy was not significantly different to placebo.

Pharmacokinetic properties:

In healthy fasting young adult volunteers, lamotrigine is rapidly and completely absorbed from the gut. The peak plasma concentration occurs 2,5 hours after oral administration. The mean elimination half-life is 29 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 medication, with a mean value of approximately 14 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and increasing to a mean of approximately 70 hours, when co-administered with sodium valproate alone (see DOSAGE AND DIRECTIONS FOR USE). Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers, there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. Lamotrigine is 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. The half-life of lamotrigine increases to mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone (see DOSAGE AND DIRECTIONS FOR USE).

Elderly: Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinical relevant extent.

After single doses, apparent clearance decreased by 12 %, from 35 ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10 %, from 41 to 37 ml/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0,39 ml/min/kg) lies within the range of the mean clearance values (0,31 to 0,65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg.

Patients with renal impairment: Twelve volunteers with chronic renal failure and another 6 individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. Mean CL/F were 0,42 ml/min/kg (chronic renal failure), 0,33 ml/min/kg (between haemodialysis), and 1,57 ml/min/kg (during haemodialysis) compared to 0,58 ml/min/kg in healthy volunteers. Mean plasma half-lives were 42,9 hours (chronic renal failure), 57,4 hours (between haemodialysis) and 13,0 hours (during haemodialysis), compared to 26,2 hours in healthy volunteers. On average, approximately 20 % (range = 5,6 to 35,1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on patients' anti-epileptic drug (AED) regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see DOSAGE AND DIRECTIONS FOR USE).

Patients with hepatic impairment: A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as control. The median apparent clearance of lamotrigine was 0,31, 0,24 or 0,10 ml/min/kg in patients with grade A, B, or C (Child-Pugh classification) hepatic impairment, respectively, compared to 0,34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with grade B or C hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

EPILEPSY:

Adults and children over 12 years: LAMICTIN 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: LAMICTIN 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: LAMICTIN is indicated as add-on treatment for seizures associated with Lennox-Gastaut syndrome.

BIPOLAR DISORDER (Adults 18 years of age and over): LAMICTIN is indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

CONTRA-INDICATIONS:

LAMICTIN is contra-indicated in individuals with known hypersensitivity to lamotrigine.

WARNINGS AND SPECIAL PRECAUTIONS:

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of LAMICTIN.

It is recommended that the physician closely monitor patients (including hepatic, renal and clotting parameters) 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 LAMICTIN.

Exceeding the recommended dose at the initiation of LAMICTIN therapy may be associated with an increased incidence of rash requiring withdrawal of therapy.

Abrupt withdrawal of LAMICTIN may provoke rebound seizures. Unless safety concerns (e.g. rash) require an abrupt withdrawal, the dose of LAMICTIN should be gradually decreased over a period of 2 weeks.

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 bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets (see DOSAGE AND DIRECTIONS FOR USE).

LAMICTIN 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 of up to 1 year, LAMICTIN did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, serum or red blood cell folate concentrations.

Skin Reactions: There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of LAMICTIN treatment. The majority of rashes are mild and self-limiting; however serious, potentially life-threatening skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported especially in children and in patients (adults and children) who also used valproate (see SIDE EFFECTS). Isolated cases have been reported after prolonged treatment (6 months).

Skin reactions in all clinical studies occurred in adults in approximately 10 % and in children 17 %. In patients on concomitant valproate, skin reactions occurred in 21 % of adults and in 34 % of children of whom, 12 % and 17 % respectively withdrew from treatment. Although the

majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death.

The estimated incidence of serious skin rashes reported as Stevens-Johnson syndrome in adults is 1 in 1 000. The risk of serious skin rashes in children is higher than in adults. Available data suggest the incidence of rashes which needed hospitalisation in children is 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 LAMICTIN and exceeding the recommended dose escalation of LAMICTIN (see DOSAGE AND DIRECTIONS FOR USE).
- Concomitant use of valproate, which increases the mean half-life of LAMICTIN nearly two-fold (see Pharmacokinetic properties and 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 LAMICTIN withdrawn immediately unless the rash is clearly not drug related. It is recommended that LAMICTIN not be restarted in patients who have discontinued due to rash associated with prior treatment with LAMICTIN.

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 multi-organ failure. It is important to note 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 LAMICTIN discontinued if an alternative aetiology cannot be immediately established.

Hormonal contraceptives:

Effects of hormonal contraceptives on LAMICTIN efficacy*:* An ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination has been demonstrated to increase the clearance of LAMICTIN by approximately two-fold resulting in decreased LAMICTIN levels (see INTERACTIONS). Following titration, higher maintenance doses of LAMICTIN (by as much as two-fold) may be needed to attain an optimum therapeutic response. In women not already taking an inducer of LAMICTIN glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. 'pill-free week'), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when LAMICTIN dose increases are made in the days before or during the week of inactive contraceptive medication. Cases of breakthrough convulsions have been reported in women also using hormonal contraceptives. For dosing instructions see 'General Dosing Recommendations for LAMICTIN in Special Patient Populations', DOSAGE AND DIRECTIONS FOR USE.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during LAMICTIN therapy and LAMICTIN dosing adjustments may be needed. Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect LAMICTIN pharmacokinetic parameters.

Effects of LAMICTIN on hormonal contraceptive efficacy: An interaction study in 16 healthy volunteers has shown that when LAMICTIN and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see INTERACTIONS). The impact of these changes on ovarian ovulatory activity is unknown. However, these changes may result in decreased contraceptive efficacy in patients taking hormonal preparations. Cases of unplanned pregnancy, metro/menorrhagia, breakthrough bleeding and amenorrhoea have been reported. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Renal failure: In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, there is accumulation of the glucuronide metabolite; caution should therefore be exercised in treating patients with renal failure.

Bipolar Disorder: The possibility of a suicide attempt is inherent in bipolar disorder and close supervision of high-risk patients should accompany drug therapy.

Effects on Ability to Drive and Use Machines: In clinical trials with LAMICTIN adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how LAMICTIN therapy affects them before driving or operating machinery.

Excipient warnings:

LAMICTIN tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take LAMICTIN tablets (see COMPOSITION).

INTERACTIONS:

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes and interactions between lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Effects of other drugs on glucuronidation of lamotrigine:

Drugs that significantly inhibit glucuronidation of lamotrigine (doubling of lamotrigine half-life)	Drugs that significantly induce glucuronidation of lamotrigine (halving lamotrigine half-life)
Valproate	Carbamazepine Phenytoin Primidone Phenobarbitone Rifampicin Ethinyloestradiol/levonorgestrel combination *

* Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Interactions involving AEDs (see DOSAGE AND DIRECTIONS FOR USE): Valproate, which inhibits the glucuronidation of lamotrigine, significantly reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain antiepileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes, induce the metabolism glucuronidation of lamotrigine and significantly enhance the metabolism of lamotrigine leading to a halving of the elimination half-life of LAMICTIN.

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 LAMICTIN. These events usually resolve when the dose of carbamazepine is reduced.

Although increases 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.

In a study in healthy adult volunteers using doses of 200 mg LAMICTIN and 1 200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine. However, other doses of either medication have not been studied, while carbamazepine halves the LAMICTIN half-life (see above).

Interactions involving other psychotopic agents: The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate, given twice daily for six days to 20 healthy subjects, were not altered by co-administration of 100 mg/day LAMICTIN.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

In vitro inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of medicine eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives:

Effect of hormonal contraceptives on lamotrigine pharmacokinetics: In a study of 16 female volunteers, 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52 % and 39 % reduction in lamotrigine AUC and C_{max}, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. 'pill-free' week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy. Breakthrough seizures have been reported in women using contraceptives.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics: In a study of 16 female volunteers, a steady state dose of 300 mg LAMICTIN had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19 % and 12 % reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see WARNINGS). The effects of doses of LAMICTIN other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted. Cases of unplanned pregnancy, menstral disorders and amenorrhoea have been reported. Any change in the menstral bleeding patterns should be reported to the physician of the patient.

Interactions involving other medications: Although there are no formal interaction studies, it has been reported in one study in 10 male volunteers that, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes

responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the treatment regimen recommended for LAMICTIN and concurrent glucuronidation inducers should be used (see DOSAGE AND DIRECTIONS FOR USE).

PREGNANCY AND LACTATION:

Safety of LAMICTIN in pregnancy and lactation has not been established.

Use during pregnancy: There are insufficient data available on the use of LAMICTIN in human pregnancy to evaluate its safety. LAMICTIN should not be used in pregnancy. Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during LAMICTIN therapy should be ensured.

Use in lactation: There is limited information on the use of LAMICTIN in lactation. Preliminary data indicate that it passes into breast milk in concentrations usually of the order of 40-60 % of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur.

DOSAGE AND DIRECTIONS FOR USE:

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

Do not exceed the maximum dosage (see WARNINGS AND SPECIAL PRECAUTIONS).

General Dosing Recommendations:

Administration: LAMICTIN Dispersible Tablets should be dispersed in a small volume of water (at least enough to cover the whole tablet). The tablets may also be chewed, or swallowed whole with a little water, if preferred.

If a calculated dose of LAMICTIN (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

Restarting Therapy: Prescribers should assess the need for escalation to maintenance dose when restarting LAMICTIN in patients who have discontinued LAMICTIN for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for LAMICTIN (see WARNINGS AND SPECIAL PRECAUTIONS). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing LAMICTIN exceeds five half-lives (see Pharmacokinetic properties), LAMICTIN should generally be escalated to the maintenance dose according to the appropriate schedule. It is recommended that LAMICTIN not be restarted in patients who have discontinued due to rash associated with prior treatment with LAMICTIN.

EPILEPSY:

When concomitant antiepileptic drugs are withdrawn to achieve LAMICTIN monotherapy or other AEDs/medications are added-on to treatment regimes containing LAMICTIN, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (*see* INTERACTIONS).

To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. If a calculated dose of LAMICTIN (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

Dosage in epilepsy monotherapy:

Adults and children over 12 years of age: The initial dose in monotherapy is 25 mg once a day for 2 weeks, followed by 50 mg once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 50 mg - 100 mg every 1-2 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 as two divided doses. Some patients have required 500 mg/day of LAMICTIN to achieve the desired response.

Dosage in epilepsy add-on therapy:

Adults and children over 12 years of age: In those patients taking concomitant antiepileptic drugs (AEDs) or other medications (see INTERACTIONS) that induce lamotrigine glucorinidation with/without other AEDs (except valproate), the initial LAMICTIN dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 100 mg 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.

In those patients taking sodium valproate with/without any other AED, the initial LAMICTIN dose is 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 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 those patients taking oxcarbazepine 1 200 mg daily, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial LAMICTIN dose is 25 mg once a day for 2 weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until optimal response is achieved or a dose of 200 mg is reached. The usual maintenance dose to achieve an optimal response is 100-200 mg/day given once a day or as two divided doses.

Table 1: Recommended treatment regimen for adults over 12 years of age

Treatment regimen		Weeks 1 + 2	Weeks 3 + 4	Maintenance Dose
Monotherapy		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
Add-on therapy with valproate regardless of any concomitant medications		12,5 mg (given as 25 mg on alternate 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
Add-on therapy without valproate	This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone, or with other inducers of lamotrigine glucuronidation (see INTERACTIONS).	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
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	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
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see INTERACTIONS), the treatment regimen as recommended for LAMICTIN with concurrent valproate should be used.				

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

Children aged 2 to 12 years: 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 bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

In those patients taking concomitant AEDs or other medications (see INTERACTIONS) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial LAMICTIN dose is 0,6 mg/kg bodymass/day given in two divided doses for 2 weeks, followed

by 1,2 mg/kg/day for 2 weeks. Thereafter, the dose should be increased by a maximum of 1,2 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. A maximum daily dose of 400 mg must not be exceeded.

In those patients taking sodium valproate with/without any other AED, the initial LAMICTIN dose is 0,15 mg/kg bodymass/day given once a day for 2 weeks, followed by 0,3 mg/kg/day given once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,3 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. A maximum daily dose of 200 mg must not be exceeded.

In patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial LAMICTIN dose is 0,3 mg/kg bodyweight/day given once a day or in two divided doses for 2 weeks, followed by 0,6 mg/kg/day given once a day or in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,6 mg/kg every 1-2 weeks until an optimal response is achieved, or a dose of 200 mg is reached. The usual maintenance dose to achieve optimal response is 1-10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

Table 2: Recommended *treatment regimen* for children aged 2-12 years (total daily dose in mg/kg bodyweight/day)

Treatment regimen		**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance Dose**
Add-on therapy with valproate regardless of any other concomitant medication		0,15 mg/kg* (once a day)	0,3 mg/kg (once a day)	0,3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin, Carbamazepine, Phenobarbitone, Primidone, or with other inducers of lamotrigine glucuronidation (see INTERACTIONS).	0,6 mg/kg (two divided doses)	1,2 mg/kg (two divided doses)	1,2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	0,3 mg/kg (one or two divided doses)	0,6 mg/kg (one or two divided doses)	0,6 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see INTERACTIONS), the treatment regimen as recommended for LAMICTIN with concurrent valproate should be used.				
* If the calculated daily dose in patients taking valproate is 1-2 mg, then 2 mg LAMICTIN may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then LAMICTIN should not be administered.				

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

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 doses used for seizures associated with Lennox-Gastaut syndrome correspond to the dosing guidelines outlined above for both adults and children aged 2-12 years.

Children aged less than 2 years: There is insufficient information on the use of LAMICTIN in children aged less than two years.

BIPOLAR DISORDER:

Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see WARNINGS AND SPECIAL PRECAUTIONS).

LAMICTIN is recommended for use in bipolar patients at risk for a future depressive episode. The following transition regimen should be followed to prevent recurrence of depressive episodes. The transition regimen involves escalating the dose of LAMICTIN to a maintenance stabilisation dose over 6 weeks (see table below) after which other psychotropic and/or anti-epileptic drugs can be withdrawn, if clinically indicated.

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with LAMICTIN in mania has not been conclusively established.

Recommended dose escalation to the maintenance total daily stabilisation dose for adults (over 18 years of age) treated for BIPOLAR DISORDER:

Treatment Regimen	Weeks 1-2	Weeks 3-4	Week 5	Target Stabilisation Dose (Week 6) **
a) Adjunct therapy with enzyme inhibitors e.g. valproate	12,5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
b) Adjunct therapy with enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking valproate	50 mg (once a day)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
c) Adjunct therapy to drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, OR monotherapy with lamotrigine	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200mg (range 100-400 mg)(once a day or two divided doses)
NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMICTIN is currently not known, the dose escalation as recommended for LAMICTIN with concurrent valproate, should be used.				
**The Target stabilisation dose will alter depending on clinical response.				

a) Adjunct therapy with enzyme inhibitors e.g. valproate: In patients taking enzyme inhibiting concomitant drugs such as valproate the initial LAMICTIN dose is 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 weeks. The dose should be increased to 50 mg once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.

b) Adjunct therapy with enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking valproate: In those patients taking enzyme inducing drugs such as carbamazepine or phenobarbitone and NOT taking valproate, the initial LAMICTIN dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. The dose should be increased to 200 mg/day given as two divided doses in week

5. The dose may be increased in week 6 to 300 mg/day however, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses which may be given from week 7.

c) **Adjunct therapy to drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, OR monotherapy with LAMICTIN:** The initial LAMICTIN dose in patients taking concomitant drugs with no known/theoretical pharmacokinetic interaction with lamotrigine or in monotherapy, is 25 mg once a day for 2 weeks, followed by 50 mg once a day (or in two divided doses) for 2 weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100-400 mg was used in clinical trials.

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule below (see table below).

Maintenance stabilisation total daily dose in BIPOLAR DISORDER following withdrawal of concomitant psychotropic or anti-epileptic drugs:

<table>
<tr><th colspan="2">Treatment Regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td colspan="2">a) Following withdrawal of enzyme inhibitors e.g. valproate</td><td>Double the stabilisation dose, not exceeding 100 mg/week

i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day</td><td colspan="2">Maintain this dose (200 mg/day)
(two divided doses)</td></tr>
<tr><td rowspan="3">b) Following withdrawal of enzyme inducers e.g. carbamazepine depending on original dose</td><td></td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td></td><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td></td><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td colspan="2">c) Following withdrawal of other psychotropic or AED drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day)
(two divided doses)
(range 100-400 mg)</td></tr>
<tr><td colspan="5">NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMICTIN is currently not known, the dose escalation as recommended for LAMICTIN with concurrent valproate, should be used.</td></tr>
<tr><td colspan="5">* Dose may be increased to 400 mg/day as needed</td></tr>
</table>

a) **Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate:**

The dose of LAMICTIN should be increased to double the original target stabilisation dose and maintained at this, once valproate has been terminated.

b) **Following withdrawal of adjunct therapy with enzyme inducers e.g. carbamazepine, depending on original maintenance dose:** The dose of LAMICTIN should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

c) **Following withdrawal of adjunct therapy with other psychotropic or anti-epileptic drugs with no known pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion:** The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

Adjustment of LAMICTIN daily dosing in patients with BIPOLAR DISORDER following addition of other medications:

There is no clinical experience in adjusting the LAMICTIN daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (see below):

Adjustment of LAMICTIN daily dosing in patients with BIPOLAR DISORDER following the addition of other medications:

<table>
<tr><th colspan="2">Treatment Regimen</th><th>Current lamotrigine stabilisation dose (mg/day)</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards</th></tr>
<tr><td rowspan="3">a)</td><td rowspan="3">Addition of enzyme inhibitors e.g. valproate, depending on original dose of LAMICTIN</td><td>200 mg</td><td>100 mg</td><td colspan="2">Maintain this dose (100 mg/day)</td></tr>
<tr><td>300 mg</td><td>150 mg</td><td colspan="2">Maintain this dose (150 mg/day)</td></tr>
<tr><td>400 mg</td><td>200 mg</td><td colspan="2">Maintain this dose (200 mg/day)</td></tr>
<tr><td rowspan="3">b)</td><td rowspan="3">Addition of enzyme inducers e.g. carbamazepine in patients NOT taking valproate and depending on original dose of LAMICTIN</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>150 mg</td><td>150 mg</td><td>225 mg</td><td>300 mg</td></tr>
<tr><td>100 mg</td><td>100 mg</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>c)</td><td>Addition of other psychotropic or AED drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day)
(range 100-400 mg)</td></tr>
<tr><td colspan="6">NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMICTIN is currently not known, the dose escalation as recommended for LAMICTIN with concurrent valproate, should be used.</td></tr>
</table>

Discontinuation of LAMICTIN in patients with bipolar disorder: In clinical trials, there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of LAMICTIN versus placebo. Therefore, patients may terminate LAMICTIN without a step-wise reduction of dose.

Children (less than 18 years of age): Safety and efficacy of LAMICTIN in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

General Dosing recommendations for LAMICTIN in Special Patient Populations:

Women taking hormonal contraceptives:

(a) ***Starting LAMICTIN in patients already taking hormonal contraceptives:*** Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS), no adjustments to the recommended dose escalation guidelines for LAMICTIN should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether LAMICTIN is added to an inhibitor of lamotrigine glucuronidation e.g. valproate; whether LAMICTIN is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampin; or whether LAMICTIN is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (see Table 1).

(b) ***Starting hormonal contraceptives in patients already taking maintenance doses of LAMICTIN and NOT taking inducers of lamotrigine glucuronidation:*** The maintenance dose of LAMICTIN may need to be increased by as much as two-fold according to the individual clinical response (see WARNINGS AND SPECIAL PRECAUTIONS & INTERACTIONS).

(c) ***Stopping hormonal contraceptives in patients already taking maintenance doses of LAMICTIN and NOT taking inducers of lamotrigine glucuronidation:***

The maintenance dose of LAMICTIN may need to be decreased by as much as 50 % according to the individual clinical response (see WARNINGS AND SPECIAL PRECAUTIONS & INTERACTIONS).

Elderly (over 65 years of age): No dosage adjustment from recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population.

Hepatic impairment: Initial, escalating and maintenance doses should generally be reduced by approximately 50 % in patients with moderate (Child-Pugh grade B) and 75 % in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

Renal impairment: Caution should be exercised when administering LAMICTIN to patients with renal failure. For patients with end-stage renal failure, initial doses of LAMICTIN should be based on patient's AED regimen; reduced maintenance doses should be used for patients with significant renal functional impairment.

SIDE EFFECTS:

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of LAMICTIN. The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000).

Epilepsy:

Skin and subcutaneous tissue disorders:

During monotherapy clinical trials:

Very common: skin rash

During other clinical experience:

Very common: skin rash

Rare: Stevens-Johnson syndrome

Very rare: toxic epidermal necrolysis

In double-blind, add-on clinical trials, skin rashes occurred in up to 10 % of patients taking LAMICTIN and in 5 % of patients taking placebo. The skin rashes led to the withdrawal of

LAMICTIN treatment in 2 % of patients. The rash, usually maculopapular in appearance, generally appears within 8 weeks of starting treatment and resolves on withdrawal of LAMICTIN (see WARNINGS AND SPECIAL PRECAUTIONS).

Serious, potentially life-threatening skin rashes, including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see WARNINGS AND SPECIAL PRECAUTIONS).

The overall risk of rash, appears to be strongly associated with high initial doses of LAMICTIN and exceeding the recommended dose escalation of LAMICTIN therapy (see DOSAGE AND DIRECTIONS FOR USE).

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see WARNINGS AND SPECIAL PRECAUTIONS).

Blood and lymphatic system disorders:

Very rare: haematological abnormalities including, anaemia, neutropenia, leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis

Haematological abnormalities may or may not be associated with a hypersensitivity syndrome (see WARNINGS AND SPECIAL PRECAUTIONS).

Immune system disorders:

Very rare: hypersensitivity syndrome* (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi-organ failure)

*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 and multiorgan failure. It is important to note 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 LAMICTIN discontinued if an alternative aetiology cannot be established (see WARNINGS AND SPECIAL PRECAUTIONS).

Psychiatric disorders:

Common: irritability

Uncommon: aggression

Very rare: tics, hallucinations, confusion

Nervous system disorders:

During monotherapy clinical trials:

Very common: headache

Common: drowsiness, insomnia, dizziness, tremor, vertigo, parasthesia

Uncommon: ataxia

During other clinical experience:

Very common: headache, dizziness

Common: nystagmus, tremor, ataxia, drowsiness, insomnia

Very rare: agitation, unsteadiness, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency

There have been reports that LAMICTIN may worsen Parkinsonian symptoms in patients with pre-existing Parkinson's disease and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders:

Very common: diplopia, blurred vision

Rare: conjunctivitis

Gastrointestinal disorders:

During monotherapy clinical trials:

Common: nausea

During other clinical experience:

Common: gastrointestinal disturbance (including vomiting and diarrhoea)

Hepatobiliary disorders:

Very rare: increased liver function tests, hepatic dysfunction, hepatic failure

Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.

Musculoskeletal and connective tissue disorders:

Very rare: Lupus-like reactions

General disorders and administration site conditions:

Common: tiredness.

Bipolar Disorder:

The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of LAMICTIN.

Skin and subcutaneous tissue disorders:

During bipolar disorder clinical trials:

Very common: skin rash

Rare: Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with LAMICTIN are considered, skin rashes occurred in 14 % of patients on LAMICTIN. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 9 % of patients taking LAMICTIN and in 8 % of patients taking placebo.

Nervous system disorders:

During bipolar disorder clinical trials:

Very common: headache

Common: agitation, somnolence, dizziness

Musculoskeletal and connective tissue disorders:

During bipolar disorder clinical trials:

Common: arthralgia

General disorders and administration site conditions:

During bipolar disorder clinical trials:

Common: pain, back pain.

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 dose 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:

LAMICTIN 25: Pale, yellowish-brown, multifaceted, superelliptical, unscored tablet, branded 'GSEC7' on one side, with '25' on the reverse.

LAMICTIN 50: Pale, yellowish-brown, multifaceted, superelliptical, unscored tablet, branded 'GSEE1' on one side, with '50' on the reverse.

LAMICTIN 100: Pale, yellowish-brown, multifaceted, superelliptical, unscored tablet, branded 'GSEE5' on one side, with '100' on the reverse.

LAMICTIN 200: Pale, yellowish-brown, multifaceted, superelliptical, unscored tablet, branded 'GSEE7' on one side, with '200' on the reverse.

LAMICTIN P2: White to off-white round tablets with a blackcurrant odour. One side has a bevelled edge and is engraved LTG over the number 2. The other side is engraved with two overlapping super-ellipses at right angles.

LAMICTIN P5: White to off-white with odour of blackcurrant. Elongated, biconvex tablets, may be scored. Branded ‘GS CL2’ on one side and ‘5’ on the reverse. The tablets may be slightly mottled.

LAMICTIN P25: White to off-white with odour of blackcurrant. Multifaceted, superelliptical, unscored. Branded ‘GSCL5’ on one side and ‘25’ on the reverse. The tablets may be slightly mottled.

LAMICTIN P50: White to off-white with odour of blackcurrant. Multifaceted, superelliptical, unscored. Branded ‘GSCX7’ on one side and ‘50’ on the reverse. The tablets may be slightly mottled.

LAMICTIN P100: White to off-white with odour of blackcurrant. Multifaceted, superelliptical, unscored. Branded ‘GSCL7’ on one side and ‘100’ on the reverse. The tablets may be slightly mottled.

LAMICTIN P200: White to off-white with odour of blackcurrant. Multifaceted, superelliptical, unscored. Branded ‘GSEC5’ on one side and ‘200’ on the reverse. The tablets may be slightly mottled.

PRESENTATION:

LAMICTIN 25: Blister pack of 60 tablets.

LAMICTIN 50: Blister pack of 60 tablets.

LAMICTIN 100: Blister pack of 60 tablets.

LAMICTIN 200: Blister pack of 60 tablets.

LAMICTIN P2: Opaque, white plastic bottle, with child-resistant closure containing 30 tablets.

LAMICTIN P5: Amber glass bottle containing 100 tablets.

LAMICTIN P25: Amber glass bottle containing 60 tablets.

LAMICTIN P50: Amber glass bottle containing 60 tablets.

LAMICTIN P100: Amber glass bottle containing 60 tablets.

LAMICTIN P200: Amber glass bottle containing 60 tablets.

STORAGE INSTRUCTIONS:

LAMICTIN Tablets (non-dispersible):

Store below 30 ºC.

Keep dry.

Keep out of reach of children.

LAMICTIN Dispersible Tablets:

Protect from light.

Store below 30 ºC.

Keep dry.

Keep out of reach of children.

REGISTRATION NUMBER:

LAMICTIN 25: Z/2.5/280

LAMICTIN 50: Z/2.5/281

LAMICTIN 100: Z/2.5/282

LAMICTIN 200: 29/2.5/0472

LAMICTIN P2: 36/2.5/0407

LAMICTIN P5: 29/2.5/0303

LAMICTIN P25: 29/2.5/0304

LAMICTIN P50: 32/2.5/0459

LAMICTIN P100: 29/2.5/0305

LAMICTIN P200: 32/2.5/0460

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

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

10 August 2007

GDS-18

LAMICTIN is a registered trade mark of the **GSK** group of companies

Botswana:

Lamictin 25 mg Tablets - Reg No BOT0700895 S2

Lamictin 50 mg Tablets - Reg No BOT0700896 S2

Lamictin 100 mg Tablets - Reg No BOT0700897 S2

Lamictin P2 - Reg No BOT1502692 S2

Lamictin P5 - Reg No BOT1502693 S2

Lamictin P25 - Reg No BOT1502694 S2

Lamictin P50 - Reg No BOT1502695 S2

Lamictin P100 - Reg No BOT1502696 S2

Lamictin P200 - Reg No BOT1502697 S2

Namibia:

Lamictin 25 mg Tablets - Reg No 04/2.5/0866 NS2

Lamictin 50 mg Tablets - Reg No 04/2.5/0867 NS2

Lamictin 100 mg Tablets - Reg No 04/2.5/0868 NS2

Lamictin 200 mg Tablets - Reg No 04/2.5/0869 NS2

Lamictin P5 mg Tablets - Reg No 04/2.5/0861 NS2

Lamictin P25 mg Tablets - Reg No 04/2.5/0862 NS2

Lamictin P50 mg Tablets - Reg No 04/2.5/0863 NS2

Lamictin P100 mg Tablets - Reg No 04/2.5/0864 NS2

Lamictin P200 mg Tablets - Reg No 04/2.5/0865 NS2

SKEDULERINGSTATUS:

S3

EIENDOMSNAAM EN DOSEERVORM:

LAMICTIN® 25, **50**, **100** en **200** Tablette

LAMICTIN® P2, **P5**, **P25**, **P50**, **P100** en **P200** Dispergeerbare Tablette

SAMESTELLING:

Elke LAMICTIN 25 tablet bevat: 25 mg lamotrigien

Bevat laktosemonohidraat (24,7 mg/tablet)

Elke LAMICTIN 50 tablet bevat: 50 mg lamotrigien

Bevat laktosemonohidraat (49,4 mg/tablet)

Elke LAMICTIN 100 tablet bevat: 100 mg lamotrigien

Bevat laktosemonohidraat (98,8 mg/tablet)

Elke LAMICTIN 200 tablet bevat: 200 mg lamotrigien

Bevat laktosemonohidraat (114,7 mg/tablet)

Mengmiddels: Die ander bestanddele van LAMICTIN tablette is laktosemonohidraat, mikrokristallyne sellulose, povidoon, natriumstyselglikolaat, ysteroksied-geel (E172) en magnesiumstearaat.

Elke LAMICTIN P2 dispergeerbare tablet bevat: 2 mg lamotrigien

Elke LAMICTIN P5 dispergeerbare tablet bevat: 5 mg lamotrigien

Elke LAMICTIN P25 dispergeerbare tablet bevat: 25 mg lamotrigien

Elke LAMICTIN P50 dispergeerbare tablet bevat: 50 mg lamotrigien

Elke LAMICTIN P100 dispergeerbare tablet bevat: 100 mg lamotrigien

Elke LAMICTIN P200 dispergeerbare tablet bevat: 200 mg lamotrigien

Mengmiddels: Die ander bestanddele van LAMICTIN dispergeerbare tablette is kalsiumkarbonaat, lae gesubstitueerde hidroksiepropielsellulose, aluminiummagnesium-silikaat, natriumstyselglikollaat, povidoon, sakkariennatrium, swartbessiegeur en magnesiumstearaat.

FARMAKOLOGIESE KLASSIFIKASIE:

A 2.5 Antikonvulsante, insluitend anti-epileptiese middels

FARMAKOLOGIESE WERKING:

Farmakodinamiese eienskappe:

Die resultate van farmakologiese proewe suggereer dat lamotrigien by spanningsensitiewe natriumkanale optree om neuronale membrane te stabiliseer en neurotransmittorvrystelling te inhibeer, veral van glutamaat, 'n opwekker aminosuur wat vermoedelik 'n sleutelrol in die opwekking van epileptiese aanvalle speel.

Kliniese doeltreffendheid in die voorkoming van depressiewe episodes in pasiënte met bipolêre siekte: Twee deurslaggewende proewe het doeltreffendheid in die voorkoming van depressiewe episodes in pasiënte met bipolêr-1-siekte, gedemonstreer.

Een was 'n veelvoudige-sentrum, dubbel-blind, dubbel-fop, plasebo- en litium-beheerde, willekeurige vaste-dosis evaluering van die langtermyn voorkoming van terugval en herhaling van depressie en/of manie in pasiënte met bipolêr-1-siekte, wat onlangs of teenswoordig 'n major depressiewe episode ondervind het. Nadat hulle met lamotrigien-monoterapie of lamotrigien plus psigotropiese medikasie gestabiliseer is, is pasiënte willekeurig toegeken aan een van vyf behandelingsgroepe: lamotrigien (50, 200, 400 mg/dag), litium (serumvlakke van

0,8 tot 1,1 mEkw/ℓ) of plasebo vir ’n maksimum van 76 weke (18 maande). Behandelingsregimens is onderhou totdat ’n gemoedstoestandepisode (depressief of manies) ontwikkel, wat intervensie met addisionele farmakoterapie of elektrokonvulsiewe terapie (EKT) genoodsaak het.

Die primêre eindpunt was ‘Tyd tot Intervensie vir ’n Gemoedstoestandepisode (TIME)’, waar die intervensies met addisionele farmakoterapie, óf EKT genoodsaak was. Hierdie eindpunt is geanaliseer deur gebruik te maak van drie metodes vir die hantering van data van pasiënte wat onttrek is voordat hulle ’n intervensie gehad het. Die p-waardes vir hierdie analises het gewissel van 0,003 tot 0,029. In ondersteunende analises van tyd tot eerste depressiewe episode en tyd tot eerste maniese/hipomaniese of gemengde episode, het pasiënte op lamotrigien langer tye as pasiënte op plasebo tot eerste depressiewe episode gehad (p = 0,047), en die verskil as gevolg van behandeling met betrekking tot tyd tot maniese/hipomaniese of gemende episodes was nie statisties beduidend nie.

’n Ander proef was ’n veelvoudige-sentrum, dubbel-blind, dubbel-fop, plasebo- en litium-beheerde, willekeurige, aanpasbare-dosis evaluering van lamotrigien in die langtermyn voorkoming van terugval en herhaling van manie en/of depressie in pasiënte met bipolêr-1-siekte wat onlangs of teenswoordig ’n maniese of hipomaniese episode ondervind het. Nadat hulle met lamotrigien-monoterapie of lamotrigien plus psigotropiese medikasie gestabiliseer is, is pasiënte willekeurig toegeken aan een van drie behandelingsgroepe: lamotrigien (100 tot 400 mg/dag), litium (serumvlakke van 0,8 tot 1,1 mEkw/ℓ) of plasebo vir ’n maksimum van 76 weke (18 maande). Behandelingsregimens is onderhou totdat ’n ontluikende gemoedstoestandepisode (depressief of manies) ontwikkel, wat intervensie met addisionele farmakoterapie of elektrokonvulsiewe terapie (EKT) genoodsaak het.

Die primêre eindpunt was ‘Tyd tot Intervensie vir ’n Gemoedstoestandepisode (TIME)’, waar die intervensies met addisionele farmakoterapie, óf EKT genoodsaak was. Hierdie eindpunt is geanaliseer deur gebruik te maak van drie metodes vir die hantering van data van pasiënte wat onttrek is voordat hulle ’n intervensie gehad het. Die p-waardes vir hierdie analises het gewissel

van 0,003 tot 0,023. In ondersteunende analises van tyd tot eerste depressiewe episode en tyd tot eerste maniese/hipomaniese of gemengde episode, het pasiënte op lamotrigien langer tye as pasiënte op plasebo tot eerste depressiewe episode gehad (p = 0,015) en die verskil as gevolg van behandeling met betrekking tot tyd tot maniese/hipomaniese of gemengde episodes was nie statisties beduidend nie.
In kliniese studies, het die neiging om destabilisering, manie of hipomanie te induseer tydens lamotrigienterapie, nie beduidend van plasebo verskil nie.

Farmakokinetiese eienskappe:

In gesonde, vastende jong volwasse vrywilligers, word lamotrigien vinnig en volledig uit die spysverteringskanaal geabsorbeer. Die piek plasmakonsentrasie word 2,5 uur na mondelikse toediening bereik. Die gemiddelde eliminasiehalfleeftyd is 29 uur en die farmakokinetiese profiel is liniêr tot by 450 mg, die hoogste enkeldosis wat getoets is. Die halfleeftyd van lamotrigien word deur gelyktydige toediening van medikasie beïnvloed, met ’n gemiddelde waarde van ongeveer 14 uur wanneer dit saam met ensiem-induserende geneesmiddels, soos karbamasepien en fenitoïen, toegedien word. Die halfleeftyd neem toe tot ’n gemiddelde van ongeveer 70 uur wanneer dit saam met natriumvalproaat alleen, toegedien word (sien DOSIS EN GEBRUIKSAANWYSINGS). Na veelvoudige toediening van lamotrigien (150 mg twee keer per dag) aan normale vrywilligers, vind ’n geringe induksie van die middel se eie metabolisme plaas, wat ’n 25 % verlaging in die eliminasiehalfleeftyd in die ewewigstoestand, veroorsaak.
55 % van lamotrigien is aan plasmaproteïene gebind. Opruiming wat vir liggaamsgewig aangepas is, is hoër in kinders van 12 jaar en jonger, as in volwassenes, en die hoogste waardes kom in kinders jonger as 5 jaar voor. Die halfleeftyd van lamotrigien is gewoonlik korter in kinders as in volwassenes met ’n gemiddelde waarde van ongeveer 7 uur wanneer dit met ensiem-induserende geneesmiddels, soos karbamasepien en fenitoïen, toegedien word. Die halfleeftyd van lamotrigien neem toe tot gemiddelde waardes van ongeveer 45 tot 55 uur

wanneer dit saam met natriumvalproaat alleen, toegedien word (sien DOSIS EN GEBRUIKSAANWYSINGS).

Bejaardes: Resultate van 'n farmakokinetiese analise van 'n bevolking wat beide jong en bejaarde epileptiese pasiënte ingesluit het, wat in dieselfde proewe ingeskryf is, het aangedui dat die opruiming van lamotrigien nie tot 'n klinies toepaslike mate verander het nie.
Na enkeldosisse het bewysbare opruiming met 12 % verminder van 35 ml/min op die ouderdom van 20, tot 31 ml/min op 70 jaar. Die afname na 48 weke van behandeling was 10 % van 41 tot 37 ml/min tussen die jonger en ouer groepe wat met mekaar vergelyk is.
Daarbenewens is die farmakokinetika van lamotrigien in 12 gesonde, bejaarde proefpersone na 'n enkele 150 mg dosis bestudeer. Die gemiddelde opruiming in bejaardes (0,39 ml/min/kg) val binne die reikwydte van die gemiddelde opruimingswaardes (0,31 tot 0,65 ml/min/kg) wat in 9 studies met nie-bejaarde volwassenes na enkeldosisse van 30 tot 450 mg verkry is.

Pasiënte met nierinkorting: 'n Enkel 100 mg dosis lamotrigien is aan elkeen van twaalf vrywilligers met chroniese nierversaking en 6 ander individue wat hemodialise ondergaan het, toegedien. Die gemiddelde CL/F was 0,42 ml/min/kg (chroniese nierversaking), 0,33 ml/min/kg (tussen hemodialise), en 1,57 ml/min/kg (tydens hemodialise) vergeleke met 0,58 ml/min/kg in gesonde vrywilligers. Gemiddelde plasmahalfleeftye was 42,9 uur (chroniese nierversaking), 57,4 uur (tussen hemodialise), en 13,0 uur (tydens hemodialise), vergeleke met 26,2 uur in gesonde vrywilligers. Gemiddeld is ongeveer 20 % (reikwydte = 5,6 tot 35,1) van die hoeveelheid lamotrigien teenwoordig in die liggaam deur 'n 4-uur hemodialise sessie verwyder. Vir hierdie pasiëntbevolking behoort aanvanklike dosisse van lamotrigien gebaseer te word op die pasiënte se anti-epileptiese geneesmiddel (AEG) regimen; verminderde onderhoudsdosisse moet in pasiënte met beduidende inkorting van nierfunksie gebruik word (sien DOSIS EN GEBRUIKSAANWYSINGS).

Pasiënte met lewerinkorting: ’n Enkeldosis farmakokinetiese studie is uitgevoer met 24 proefpersone wat aan wisselende grade van lewerinkorting gely het, en 12 gesonde proefpersone wat as kontrolegroep opgetree het. Die mediaan bewysbare opruiming van lamotrigien was onderskeidelik 0,31, 0,24, of 0,10 ml/min/kg in pasiënte met graad A, B of C (Child-Pugh-klassifisering) lewerinkorting, vergeleke met 0,34 ml/min/kg in die gesonde kontrolegroep. Verminderde dosisse behoort oor die algemeen in pasiënte met graad B of C lewerinkorting gebruik te word (sien DOSIS EN GEBRUIKSAANWYSINGS).

INDIKASIES:

EPILEPSIE:

Volwassenes en kinders ouer as 12 jaar: LAMICTIN word as monoterapie, of aanvullende behandeling van gedeeltelike epilepsie met, of sonder, sekondêre, veralgemeende tonies-kloniese aanvalle, en in primêre veralgemeende tonies-kloniese aanvalle, aangedui.

Kinders van 2 tot 12 jaar: LAMICTIN word as aanvullende behandeling aangedui vir gedeeltelike epilepsie met, of sonder, sekondêre, veralgemeende tonies-kloniese aanvalle, wat nie bevredigend met ander anti-epileptiese medisyne beheer kan word nie.
Monoterapie in kinders jonger as 12 jaar word nie aanbeveel nie totdat voldoende inligting uit beheerde proewe in hierdie spesifieke teikenbevolking beskikbaar gemaak word.

Lennox-Gastaut-sindroom: LAMICTIN word aangedui as aanvullende behandeling van aanvalle wat met Lennox-Gastaut-sindroom geassosieer word.

BIPOLÊRE SIEKTE (Volwassenes van 18 jaar en ouer): LAMICTIN word vir die voorkoming van gemoedstoestandepisodes in pasiënte met bipolêre siekte, hoofsaaklik deur voorkoming van depressiewe episodes, aangedui.

KONTRA-INDIKASIES:

LAMICTIN is teenaangedui in persone met bekende hipersensitiwiteit teen lamotrigien.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:

Ernstige konvulsiewe aanvalle, insluitend status epilepticus, mag lei tot rabdomiolise, veelvoudige orgaanwanfunksie, en gedissemineerde intravaskulêre stolling, gewoonlik met noodlottige gevolge. Soortgelyke gevalle het in assosiasie met die gebruik van LAMICTIN voorgekom.

Dit word aanbeveel dat die geneesheer pasiënte versigtig moniteer (insluitend hepatiese, renale en stollingsparameters), wat enige kombinasie van akute, onverklaarde veluitslag, koors, griepagtige simptome, slaperigheid of verslegting in die beheer van aanvalle, veral binne die eerste maand na begin van behandeling met LAMICTIN, ontwikkel.

Oorskryding van die aanbevole dosis aan die begin van LAMICTIN-terapie mag geassosieer word met ’n toename in die voorkoms van veluitslag wat onttrekking van terapie mag noodsaak.

Skielike onttrekking van LAMICTIN mag terugslag-aanvalle uitlok. Tensy veiligheidsoorwegings (bv. veluitslag) vinnige onttrekking noodsaak, behoort die dosis LAMICTIN geleidelik oor ’n tydperk van 2 weke verminder te word.

Om te verseker dat ’n terapeutiese dosis onderhou word, moet die gewig van ’n kind gemoniteer word en die dosis moet heroorweeg word soos veranderings in gewig plaasvind.

Indien die dosisse wat vir kinders volgens liggaamsgewig bereken word, nie ooreenstem met heel tablette nie, is die dosis wat toegedien moet word, gelyk aan die laer getal heel tablette (sien DOSIS EN GEBRUIKSAANWYSINGS).

LAMICTIN is ’n swak inhibeerder van dihidrofolaatreduktase en daar bestaan dus ’n moontlikheid dat die middel met folaatmetabolisme tydens langtermyn behandeling, mag inmeng. Gedurende langtermyn menslike dosering wat tot 1 jaar geduur het, is egter geen beduidende veranderings in die hemoglobienkonsentrasie, gemiddelde

bloedliggaampievolume, of die folaatkonsentrasies in serum of rooibloedselle, deur LAMICTIN veroorsaak nie.

Velreaksies: Berigte is ontvang van nadelige velreaksies wat meestal binne die eerste 8 weke na begin van LAMICTIN-behandeling, voorgekom het. Die meerderheid van veluitslae is matig van aard en self-beperkend; maar ernstige, potensieel lewensgevaarlike veluitslae, insluitend Stevens-Johnson-sindroom en toksiese epidermale nekrolise is veral in kinders en in pasiënte (volwassenes en kinders) wat ook valproaat gebruik het, aangemeld (sien NEWE-EFFEKTE). Geïsoleerde gevalle is ook na langdurige behandeling (6 maande), gerapporteer.
Velreaksies in alle kliniese studies het in ongeveer 10 % van volwassenes, en 17 % van kinders voorgekom. By pasiënte wat gelyktydig valproaat ontvang, het velreaksies in 21 % van volwassenes, en 34 % van kinders voorgekom, waarvan 12 % en 17 % onderskeidelik van behandeling onttrek is. Alhoewel die meerderheid herstel wanneer die geneesmiddel onttrek word, ondervind sommige pasiënte onomkeerbare letselvorming en seldsame gevalle van geassosieerde sterftes het voorgekom.
Die beraamde voorkoms van ernstige veluitslae wat as Stevens-Johnson-sindroom in volwassenes gerapporteer is, was 1 uit 1 000. Die risiko van ernstige veluitslae in kinders is hoër as in volwassenes. Beskikbare data suggereer dat die voorkoms van veluitslae wat hospitalisering in kinders benodig het, wissel tussen 1 uit 300, tot 1 uit 100.

In kinders kan die aanvanklike voorkoms van ’n veluitslag met ’n infeksie verwar word; in kinders wat simptome van veluitslag en koors binne die eerste agt weke van behandeling ontwikkel, behoort geneeshere die moontlikheid van ’n geneesmiddelreaksie te oorweeg.
Daarbenewens blyk dit dat die algehele risiko van veluitslag sterk verband hou met:

- Hoë aanvanklike dosisse van LAMICTIN en oorskryding van die aanbevole dosisverhoging van LAMICTIN (sien DOSIS EN GEBRUIKSAANWYSINGS).
- Gelyktydige gebruik van valproaat, wat die gemiddelde halfleeftyd van LAMICTIN ongeveer verdubbel (sien Farmakokinetiese eienskappe en DOSIS EN GEBRUIKSAANWYSINGS).

Omdat dit nie betroubaar voorspel kan word watter veluitslae lewensgevaarlik gaan wees nie, moet alle pasiënte (volwassenes en kinders) wat 'n veluitslag ontwikkel, onmiddellik geëvalueer word, en LAMICTIN moet onmiddellik onttrek word tensy die veluitslag duidelik nie geneesmiddel-verwant is nie. Dit word aanbeveel dat LAMICTIN nie weer begin word nie in pasiënte wat gestaak het as gevolg van veluitslag geassosieer met vorige behandeling met LAMICTIN.

Veluitslag is ook al as deel van 'n hipersensitiwiteitsindroom aangemeld wat met 'n wisselende patroon van sistemiese simptome insluitend koors, limfadenopatie, pruritus, edeem van die gesig, abnormaliteite van die bloed en lewer, en trombositopenie, geassosieer word. Die sindroom toon 'n wye spektrum van kliniese erns en dit mag lei tot gedissemineerde intravaskulêre stolling en veelvoudige orgaanversaking. Dit is belangrik om daarvan bewus te wees dat vroeë tekens van hipersensitiwiteit (bv. koors, limfadenopatie), in die afwesigheid van die veluitslag, teenwoordig mag wees. Indien sulke tekens en simptome teenwoordig is, moet die pasiënt onmiddellik geëvalueer, en LAMICTIN gestaak word, indien 'n alternatiewe etiologie nie onmiddellik vasgestel kan word nie.

Hormonale voorbehoedmiddels:

Effekte van hormonale voorbehoedmiddels op LAMICTIN-doeltreffendheid: Daar kon gedemonstreer word dat 'n etinielestradiol/levonorgestrel (30 µg/150 µg)-kombinasie die opruiming van LAMICTIN ongeveer tweevoudig verhoog het, wat verminderde LAMICTIN-vlakke tot gevolg gehad het (sien INTERAKSIES). Na titrasie mag hoër onderhoudsdosisse van LAMICTIN (soveel as twee keer hoër) nodig wees om 'n optimale terapeutiese respons te bereik. In vrouens wat nog nie 'n induseerder van LAMICTIN-glukuronidasie neem nie en 'n hormonale voorbehoedmiddel neem wat een week van onaktiewe medikasie insluit (bv. 'pil-vrye week'), sal geleidelike verbygaande verhogings in lamotrigienvlakke tydens die week van onaktiewe medikasie voorkom. Hierdie verhogings sal groter wees wanneer verhogings in die LAMICTIN-dosis gemaak word in die dae voor of tydens die week van onaktiewe

kontraseptiewe medikasie . Gevalle van deurbraak-konvulsies is aangemeld in vrouens wat ook hormonale voorbehoedmiddels gebruik. Vir doseringsaanwysings sien ‘Algemene Doseringsaanbevelings vir LAMICTIN in Spesiale Pasiëntbevolkings,’ DOSIS EN GEBRUIKSAANWYSINGS.

Kliniese geneeshere behoort toepaslike kliniese beheer van vrouens wat hormonale voorbehoedmiddels begin of staak tydens LAMICTIN-terapie uit te oefen en dosisaanpassings van LAMICTIN mag nodig wees. Ander behandelings met orale voorbehoedmiddels en hormoonvervangingsterapie (HVT) is nie bestudeer nie, alhoewel hulle ’n soortgelyke effek op die farmakokinetiese parameters van LAMICTIN mag hê.

Effekte van LAMICTIN op hormonale voorbehoedmiddeldoeltreffendheid: ’n Interaksie proef met 16 gesonde vrywilligers het aangedui dat wanneer LAMICTIN en ’n hormonale voorbehoedmiddel (etinielestradiol/levonorgestrel-kombinasie) in kombinasie toegedien word, ’n klein toename in levonorgestrelopruiming en veranderings in serum-FSH en -LH voorkom (sien INTERAKSIES). Die impak van hierdie veranderings op die ovulasie aktiwiteit van die eierstokke is onbekend. Hierdie veranderings mag egter verminderde kontraseptiewe doeltreffendheid veroorsaak in pasiënte wat hormonale preparate neem. Gevalle van ongewenste swangerskap, metro-/menoragie, deurbraakbloeding en amenoree is aangemeld. Pasiënte behoort dus instruksies te ontvang om veranderings in hulle menstruele patroon, d.i. deurbraakbloeding, onmiddellik aan te meld.

Nierversaking: In enkeldosis-studies by proefpersone met endstadium-nierversaking, was plasmakonsentrasies van lamotrigien nie beduidend verander nie. ’n Ophoping van die glukuroniedmetaboliet kom egter voor; omsigtigheid moet dus uitgeoefen word wanneer pasiënte met nierversaking behandel word.

Bipolêre Versteuring: Die moontlikheid van pogings tot selfmoord is inherent in bipolêre versteuring en noukeurige toesig van hoë-risiko pasiënte behoort geneesmiddelterapie te vergesel.

Effekte op die Vermoë om te Bestuur en Masjiene te Gebruik: Nadelige insidente met 'n neurologiese karakter soos duiseligheid en diplopie is in kliniese studies met LAMICTIN aangemeld. Pasiënte behoort dus te kyk hoe LAMICTIN-terapie hulle affekteer voordat hulle bestuur of masjiene gebruik.

Mengmiddelwaarskuwings:

LAMICTIN tablette bevat laktosemonohidraat. Pasiënte met seldsame oorgeërfde probleme van galaktose-intoleransie, die Lapland-laktasegebrek of glukose-galaktosewanabsorbsie behoort nie LAMICTIN tablette te neem nie (sien SAMESTELLING).

INTERAKSIES:

UDP-glukuronieltransferases is geïdentifiseer as die ensieme wat vir die metabolisme van lamotrigien verantwoordelik is. Daar bestaan geen bewyse dat lamotrigien klinies beduidende induksie of inhibisie van hepatiese oksidatiewe geneesmiddel-metaboliserende ensieme veroorsaak nie en interaksies tussen lamotrigien en geneesmiddels wat deur sitochroom P450-ensieme gemetaboliseer word, sal waarskynlik nie voorkom nie. Lamotrigien mag sy eie metabolisme induseer, maar die effek is matig van aard en dit is onwaarskynlik dat dit beduidende kliniese gevolg sal hê.

Effekte van ander geneesmiddels op glukuronidasie van lamotrigien:

Geneesmiddels wat glukuronidasie van lamotrigien beduidend inhibeer (verdubbeling van die halfleeftyd van lamotrigien)	Geneesmiddels wat glukuronidasie van lamotrigien beduidend induseer (halvering van die halfleeftyd van lamotrigien)
Valproaat	Karbamasepien Fenitoïen Primidoon Fenobarbitoon Rifampisien Etinielestradiol/levonorgestrel-kombinasie*

* Ander mondelikse voorbehoedmiddels en HVT-behandelings is nie bestudeer nie, alhoewel hulle die farmakokinetiese parameters van lamotrigien soortgelyk mag beïnvloed.

Interaksies wat AEGs betrek (sien DOSIS EN GEBRUIKSAANWYSINGS): Valproaat, wat die inhibisie van glukuronidasie van lamotrigien inhibeer, verminder die metabolisme van lamotrigien beduidend en verhoog die gemiddelde halfleeftyd van lamotrigien amper tweevoudig.

Sekere anti-epileptiese middels (soos fenitoïen, karbamasepien, fenobarbitoon en primidoon) wat hepatiese geneesmiddel-metaboliserende ensieme induseer, induseer ook die glukuronidasie van lamotrigien en versterk die metabolisme van lamotrigien beduidend wat tot halvering van die eliminasiehalfleeftyd van LAMICTIN lei.

Berigte is ontvang van sentrale senusisteem insidente insluitend duiseligheid, ataksie, diplopie, versteurde visie en naarheid in pasiënte wat karbamasepien neem na die instelling van LAMICTIN. Hierdie insidente verdwyn gewoonlik as die dosis karbamasepien verminder word.

Alhoewel verhogings in die plasmakonsentrasies van ander anti-epileptiese geneesmiddels aangemeld is, het beheerde studies geen bewyse gelewer dat lamotrigien die plasmakonsentrasies van anti-epileptiese geneesmiddels wat gelyktydig toegedien word, beïnvloed nie. Bewyse van *in vitro* proewe dui aan dat lamotrigien nie ander anti-epileptiese geneesmiddels by proteïenbindingsetels verdring nie.

In ’n proef met gesonde, volwasse vrywilligers wat dosisse van 200 mg LAMICTIN en 1 200 mg okskarbasepien gebruik het, het okskarbasepien nie die metabolisme van lamotrigien verander, en lamotrigien het ook nie die metabolisme van okskarbasepien verander nie. Ander

dosisse van hierdie twee medisyne is egter nie bestudeer nie, terwyl karbamasepien die halfleeftyd van LAMICTIN halveer (sien bo).

Interaksies wat ander psigotopiese middels betrek: Die farmakokinetika van litium nadat 2 g watervrye litiumglukonaat twee keer per dag vir ses dae aan 20 gesonde proefpersone toegedien is, is nie deur gelyktydige toediening van 100 mg LAMICTIN per dag verander nie. Veelvoudige mondelikse dosisse van bupropioon het geen statisties beduidende effekte op die enkeldosis-farmakokinetika van lamotrigien in 12 proefpersone gehad nie en het slegs 'n effense verhoging in die AOK van lamotrigienglukuronied veroorsaak.
In vitro inhibisie-eksperimente het aangedui dat die vorming van die primêre metaboliet van lamotrigien, die 2-N-glukuronied, minimaal verander is deur gelyktydige inkubasie met amitriptilien, bupropioon, klonasepam, fluoksetien, haloperidol, of lorasepam. Data oor die metabolisme van bufuralol verkry van menslike lewermikrosome het gesuggereer dat lamotrigien nie die opruiming van geneesmiddels wat hoofsaaklik deur CYP2D6 geëlimineer word, verminder nie. Resultate van *in vitro* eksperimente suggereer ook dat dit onwaarskynlik is dat opruiming van lamotrigien deur klosapien, fenelsien, risperidoon, sertralien of trasodoon beïnvloed sal word.

Interaksies wat hormonale voorbehoedmiddels betrek:

Effek van hormonale voorbehoedmiddels op die farmakokinetika van lamotrigien: In 'n proef van 16 vroulike vrywilligers, het 30 µg etinielestradiol/150 µg levonorgestrel in 'n gekombineerde mondelikse kontraseptiewe pil 'n ongeveer tweevoudige toename in die mondelikse opruiming van lamotrigien veroorsaak, wat onderskeidelik gemiddelde verminderings van 52 % en 39 % in die AOK en K_{maks} van lamotrigien tot gevolg gehad het. Serumlamotrigienkonsentrasies het geleidelik toegeneem met verloop van die week van onaktiewe medikasie (bv. 'pil-vrye' week), terwyl pre-dosis konsentrasies aan die einde van die

week van onaktiewe medikasie, gemiddeld ongeveer twee keer hoër was as tydens gelyktydige terapie. Deurbraak-aanvalle is aangemeld in vroue wat voorbehoedmiddels gebruik het.

Effek van lamotrigien op die farmakokinetika van hormonale voorbehoedmiddels: In 'n proef van 16 vroulike vrywilligers, het 'n ewewigsdosis van 300 mg LAMICTIN geen effek op die farmakokinetika van die etinielestradiolkomponent van 'n gekombineerde mondelikse kontraseptiewe pil gehad nie. 'n Klein toename in mondelikse opruiming van die levonorgestrelkomponent is waargeneem wat onderskeidelik gemiddelde afnames van 19 % en 12 % in die AOK en K_{maks} van levonorgestrel tot gevolg gehad het. Meting van serum-FSH, -LH en -estradiol tydens die studie het 'n mate van verlies aan onderdrukking van die ovariale hormonale aktiwiteit in sommige vrouens aangedui, alhoewel meting van serumprogesteroon aangedui het dat geen hormonale bewyse van ovulasie in enigeen van die 16 proefpersone voorgekom het nie. Die impak van die klein toename in levonorgestrelopruiming en die veranderings in serum-FSH en -LH op ovariale ovulasie-aktiwiteit is onbekend (sien WAARSKUWINGS). Die effekte van ander dosisse LAMICTIN benewens 300 mg/dag is nie bestudeer nie en proewe met ander vroulike hormonale preparate is nie uitgevoer nie. Gevalle van onbeplande swangerskap, menstruele versteurings, en amenoree is aangemeld. Enige verandering in die menstruele bloedingspatrone moet aan die pasiënt se geneesheer gerapporteer word.

Interaksies wat ander medikasies betrek: Alhoewel daar geen formele interaksie proewe bestaan nie, is daar in een proef met 10 manlike vrywilligers aangemeld dat rifampisien lamotrigienopruiming verhoog het, en die halfleeftyd van lamotrigien verminder het, as gevolg van induksie van die hepatiese ensieme wat vir glukuronidasie verantwoordelik is. In pasiënte wat gelyktydige terapie met rifampisien ontvang, moet die behandelingsregimen gebruik word wat vir LAMICTIN en gelyktydige induseerders van glukuronidasie aanbeveel word (sien DOSIS EN GEBRUIKSAANWYSINGS).

SWANGERSKAP EN LAKTASIE:

Die veiligheid van LAMICTIN in swangerskap en laktasie is nie vasgestel nie.

Gebruik tydens swangerskap: Daar is onvoldoende data beskikbaar oor die gebruik van LAMICTIN in menslike swangerskap om die veiligheid daarvan te evalueer. LAMICTIN behoort nie in swangerskap gebruik te word nie.
Fisiologiese veranderings tydens swangerskap mag lamotrigienvlakke en/of die terapeutiese effek beïnvloed. Berigte van verminderde lamotrigienvlakke tydens swangerskap is ontvang. Toepaslike kliniese beheer van swanger vrouens tydens LAMICTIN-terapie moet verseker word.

Gebruik in laktasie: Beperkte inligting is tans beskikbaar oor die gebruik van LAMICTIN in laktasie. Voorlopige data dui daarop dat die middel in borsmelk voorkom in konsentrasies wat gewoonlik gelyk is aan 40-60 % van die serumkonsentrasie. In ’n klein aantal suigelinge waar dit bekend was dat hulle borsvoeding ontvang het, het die serumkonsentrasies van lamotrigien vlakke bereik waar farmakologiese effekte mag voorkom.

DOSIS EN GEBRUIKSAANWYSINGS:

Dit is belangrik om die aanbevole doserings te gebruik veral in kombinasieterapie met valproaat waar een-tiende tot een-vyfde van die normale dosis gebruik word.
Moenie die maksimum dosering oorskry nie (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Algemene Doseringsaanbevelings:

Toediening: LAMICTIN Dispergeerbare Tablette behoort in ’n klein volume water (ten minste genoeg om die hele tablet te bedek) gedispergeer te word. Die tablette mag ook gekou, of heel ingesluk word met ’n bietjie water, indien dit verkies word.
Indien ’n berekende dosis LAMICTIN (bv. vir gebruik in kinders of pasiënte met hepatiese inkorting), nie ooreenstem met heel tablette nie, is die dosis wat toegedien moet word, gelyk aan die laer getal heel tablette.

Hervatting van Terapie: Voorskrywers moet die noodsaaklikheid vir verhoging tot die onderhoudsdosis evalueer wanneer LAMICTIN hervat word in pasiënte wat LAMICTIN vir enige rede gestaak het, aangesien die risiko van ernstige veluitslag met hoë aanvangsdosisse en oorskryding van die aanbevole dosisverhoging vir LAMICTIN geassosieer word (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS). Hoe groter die tussenpose sedert die vorige dosis, hoe meer oorweging moet geskenk word aan verhoging tot die onderhoudsdosis. As die tussenpose sedert staking van LAMICTIN vyf halfleeftye oorskry (sien Farmakokinetiese eienskappe), behoort LAMICTIN in die algemeen, volgens die toepaslike skedule tot die onderhoudsdosis verhoog te word. Dit word aanbeveel dat LAMICTIN nie weer begin moet word nie in pasiënte wat gestaak het as gevolg van ’n veluitslag geassosieer met vorige behandeling met LAMICTIN.

EPILEPSIE:

Wanneer gelyktydige anti-epileptiese geneesmiddels onttrek word om LAMICTIN monoterapie te bereik of ander AEGs/medikasies by behandelingsregimens wat LAMICTIN bevat, bygevoeg word, moet oorweging geskenk word aan die effek wat dit op die farmakokinetika van lamotrigien mag hê (sien INTERAKSIES).
Om te verseker dat ’n terapeutiese dosis onderhou word, moet die gewig van ’n kind gemoniteer word en die dosis moet heroorweeg word soos veranderings in gewig plaasvind.

Indien ŉ berekende dosis van LAMICTIN (bv. vir gebruik in kinders of pasiënte met hepatiese inkorting), nie ooreenstem met heel tablette nie, is die dosis wat toegedien moet word, gelyk aan die laer getal heel tablette.

Dosering in epilepsie-monoterapie:

Volwassenes en kinders ouer as 12 jaar: Die aanvanklike dosis in monoterapie is 25 mg een keer per dag vir 2 weke, gevolg deur 50 mg een keer per dag vir 2 weke. Daarna behoort die dosis met ŉ maksimum van 50 mg - 100 mg elke 1-2 weke verhoog te word, totdat ŉ optimale respons verkry word. Die algemene onderhoudsdosis om optimale respons te bereik, is 100-200 mg/dag wat een keer per dag, of as twee verdeelde dosisse gegee word. Sommige pasiënte het tot 500 mg/dag van LAMICTIN benodig om die gewenste respons te bereik.

Dosering in epilepsie byvoegterapie:

Volwassenes en kinders ouer as 12 jaar: In daardie pasiënte wat gelyktydige anti-epileptiese geneesmiddels (AEGs) of ander medikasies (sien INTERAKSIES) neem wat glukuronidasie van lamotrigien induseer met/sonder ander AEGs (behalwe valproaat), is die aanvanklike LAMICTIN-dosis 50 mg een keer per dag vir 2 weke, gevolg deur 100 mg/dag in twee verdeelde dosisse vir 2 weke.

Daarna behoort die dosis met ŉ maksimum van 100 mg, elke 1-2 weke verhoog te word, totdat die optimale respons verkry is. Die gebruiklike onderhoudsdosis om optimale respons te bereik, is 200-400 mg/dag wat in twee verdeelde dosisse gegee word.

In daardie pasiënte wat natriumvalproaat met/sonder enige ander AEG neem, is die aanvanklike LAMICTIN dosis 25 mg elke tweede dag vir 2 weke, gevolg deur 25 mg een keer per dag vir 2 weke. Daarna behoort die dosis met ŉ maksimum van 25-50 mg elke 1-2 weke verhoog te word, totdat die optimale respons verkry is. Die gebruiklike onderhoudsdosis om optimale respons te bereik, is 100-200 mg/dag wat een keer per dag, of in twee verdeelde dosisse gegee word.

In daardie pasiënte wat okskarbasepien 1 200 mg daagliks neem, met of sonder ander induseerders of inhibeerders van lamotrigienglukuronidasie, is die aanvanklike LAMICTIN-dosis 25 mg een keer per dag vir 2 weke, gevolg deur 50 mg een keer per dag vir 2 weke. Daarna behoort die dosis met ’n maksimum van 50-100 mg elke 1-2 weke verhoog te word, totdat die optimale respons verkry is, of ’n dosis van 200 mg bereik is. Die gebruiklike onderhoudsdosis om optimale respons te bereik, is 100-200 mg/dag wat een keer daagliks of in twee verdeelde dosisse gegee word.

Tabel 1: Aanbevole behandelingsregimen vir volwassenes ouer as 12 jaar

<table>
<tr><th colspan="2">Behandelingsregimen</th><th>Weke 1 + 2</th><th>Weke 3 + 4</th><th>Onderhoudsdosis</th></tr>
<tr><td colspan="2">Monoterapie</td><td>25 mg (een keer daagliks)</td><td>50 mg (een keer daagliks)</td><td>100-200 mg (een keer daagliks of twee verdeelde dosisse)

Om onderhoud te bereik, mag dosisse met 50-100 mg elke 1-2 weke verhoog word</td></tr>
<tr><td colspan="2">Byvoegterapie met valproaat, afgesien van enige ander gelyktydige medikasies</td><td>12,5 mg (wat as 25 mg op alternatiewe dae gegee word)</td><td>25 mg (een keer daagliks)</td><td>100-200 mg (een keer daagliks of twee verdeelde dosisse)

Om onderhoud te bereik, mag dosisse met 25-50 mg elke 1-2 weke verhoog word</td></tr>
<tr><td rowspan="2">Byvoeg-terapie sonder valproaat</td><td>Hierdie doseringsregimen behoort gebruik te word met: fenitoïen, karbamasepien, fenobarbitoon, primidoon, of met ander induseerders van lamotrigien-glukuronidasie (sien INTERAKSIES)</td><td>50 mg (een keer daagliks)</td><td>100 mg (twee verdeelde dosisse)</td><td>200-400 mg (twee verdeelde dosisse)

Om onderhoud te bereik, mag dosisse met 100 mg elke 1-2 weke verhoog word</td></tr>
<tr><td>Met okskarbasepien sonder induseerders of inhibeerders van lamotrigien-glukuronidasie</td><td>25 mg (een keer daagliks)</td><td>50 mg (een keer daagliks)</td><td>100-200 mg (een keer daagliks of twee verdeelde dosisse)

Om onderhoud te bereik, mag dosisse met 50-100 mg elke 1-2 weke verhoog word</td></tr>
<tr><td colspan="5">In pasiënte wat AEGs neem waar die farmakokinetiese interaksie met lamotrigien tans nie bekend is nie (sien INTERAKSIES), behoort die behandelingsregimen soos aanbeveel vir LAMICTIN saam met gelyktydige valproaat gebruik te word.</td></tr>
</table>

Die aanbevole aanvangsdosis en daaropvolgende dosisverhoging behoort nie oorskry te word nie om die risiko van veluitslae tot ’n minimum te beperk (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Kinders van 2 tot 12 jaar: Om te verseker dat ’n terapeutiese dosis onderhou word, moet die gewig van ’n kind gemoniteer word en die dosis moet heroorweeg word soos veranderings in gewig plaasvind. Indien die dosisse wat vir kinders volgens liggaamsgewig bereken word, nie ooreenstem met heel tablette nie, is die dosis wat toegedien moet word, gelyk aan die laer getal heel tablette.

In daardie pasiënte wat gelyktydige AEGs of ander medikasies neem (sien INTERAKSIES) wat lamotrigienglukuronidasie induseer met/sonder ander AEGs (behalwe valproaat), is die aanvangsdosis van LAMICTIN 0,6 mg/kg liggaamsmassa/dag wat in twee verdeelde dosisse vir 2 weke gegee word, gevolg deur 1,2 mg/kg/dag vir 2 weke. Daarna behoort die dosis met ’n maksimum van 1,2 mg/kg elke 1-2 weke verhoog te word totdat die optimale respons verkry word. Die gebruiklike onderhoudsdosis om die optimale respons te bereik, is 5-15 mg/kg/dag wat in twee verdeelde dosisse gegee word. ’n Maksimum daaglikse dosis van 400 mg mag nie oorskry word nie.

In daardie pasiënte wat natriumvalproaat met/sonder enige ander AEG neem, is die aanvangsdosis van LAMICTIN 0,15 mg/kg liggaamsmassa/dag wat een keer per dag vir 2 weke gegee word, gevolg deur 0,3 mg/kg/dag wat een keer per dag vir 2 weke gegee word. Daarna behoort die dosis met ’n maksimum van 0,3 mg/kg elke 1-2 weke verhoog te word totdat die optimale respons verkry word. Die gebruiklike onderhoudsdosis om die optimale respons te bereik, is 1-5 mg/kg/dag wat een keer per dag, of in twee verdeelde dosisse gegee word. ’n Maksimum daaglikse dosis van 200 mg mag nie oorskry word nie.

In pasiënte wat okskarbasepien neem sonder enige induseerders of inhibeerders van lamotrigienglukuronidasie, is die aanvangsdosis van LAMICTIN 0,3 mg/kg liggaamsgewig/dag wat een keer per dag of in twee verdeelde dosisse vir 2 weke gegee word, gevolg deur

0,6 mg/kg/dag wat een keer per dag of in twee verdeelde dosisse vir 2 weke gegee word. Daarna moet die dosis met ’n maksimum van 0,6 mg/kg elke 1-2 weke verhoog word totdat ’n optimale respons verkry word, of ’n dosis van 200 mg bereik word. Die gebruiklike onderhoudsdosis om optimale respons te bereik is 1-10 mg/kg/dag wat een keer per dag of in twee verdeelde dosisse gegee word, met ’n maksimum van 200 mg/dag.

Tabel 2: Aanbevole *behandelingsregimen* vir kinders van 2-12 jaar (totale daaglikse dosis in mg/kg liggaamsgewig/dag)

Behandelingsregimen		**Weke 1 + 2**	**Weke 3 + 4**	**Onderhoudsdosis**
Byvoegterapie met valproaat afgesien van enige ander gelyktydige medikasie		0,15 mg/kg* (een keer daagliks)	0,3 mg/kg (een keer daagliks)	0,3 mg/kg inkremente elke 1-2 weke om 'n onderhoudsdosis van 1-5 mg/kg te bereik (een keer per dag of twee verdeelde dosisse) tot 'n maksimum van 200 mg/dag.
Byvoegterapie sonder valproaat	Hierdie doseringsregimen behoort gebruik te word met: Fenitoïen, Karbamasepien, Fenobarbitoon, Primidoon, of met ander induseerders van lamotrigien-glukuronidasie (sien INTERAKSIES).	0,6 mg/kg (twee verdeelde dosisse)	1,2 mg/kg (twee verdeelde dosisse)	1,2 mg/kg inkremente elke 1-2 weke om 'n onderhoudsdosis van 5-15 mg/kg te bereik (een keer per dag of twee verdeelde dosisse) tot 'n maksimum van 400 mg/dag
	Met okskarbasepien sonder induseerders of inhibeerders van lamotrigien-glukuronidasie	0,3 mg/kg (een of twee verdeelde dosisse)	0,6 mg/kg (een of twee verdeelde dosisse)	0,6 mg/kg inkremente elke 1-2 weke om 'n onderhoudsdosis van 1-10 mg/kg te bereik (een keer per dag of twee verdeelde dosisse) tot 'n maksimum van 200 mg/dag
In pasiënte wat AEGs neem waar die farmakokinetiese interaksie met lamotrigien tans nie bekend is nie (sien INTERAKSIES), behoort die behandelingsregimen soos aanbeveel vir LAMICTIN saam met gelyktydige valproaat gebruik te word.				
* Indien die berekende daaglikse dosis in pasiënte wat valproaat neem 1-2 mg is, dan mag 2 mg LAMICTIN op alternatiewe dae vir die eerste twee weke geneem word. Indien die berekende daaglikse dosis minder as 1 mg is, dan behoort LAMICTIN nie toegedien te word nie.				

Die aanbevole aanvangsdosis en daaropvolgende dosisverhoging behoort nie oorskry te word nie om die risiko van veluitslae tot 'n minimum te beperk (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Pasiënte van 2-6 jaar mag 'n onderhoudsdosis aan die hoër kant van die aanbevole reikwydte benodig.

Dosering in aanvalle wat met Lennox-Gastaut-sindroom geassosieer word: Die dosisse wat gebruik word vir aanvalle wat met Lennox-Gastaut-sindroom geassosieer word, stem ooreen met die doseringsriglyne wat hierbo vir volwassenes, asook kinders tussen die ouderdom van 2-12 jaar, beskryf is.

Kinders jonger as 2 jaar: Daar is onvoldoende inligting oor die gebruik van LAMICTIN in kinders jonger as twee jaar beskikbaar.

BIPOLÊRE SIEKTE:

As gevolg van die risiko van veluitslag, moet die aanvangsdosis en daaropvolgende dosisverhoging nie oorskry word nie (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

LAMICTIN word aanbeveel vir gebruik in bipolêre pasiënte wat aan die risiko van 'n toekomstige depressiewe episode blootgestel is.

Die volgende oorgangsregimen behoort gevolg te word om herhaling van depressiewe episodes te verhoed. Die oorgangsregimen behels verhoging van die dosis LAMICTIN tot 'n stabilisering-onderhoudsdosis oor 6 weke (sien tabel hierna), waarna ander psigotropiese en/of anti-epileptiese geneesmiddels onttrek kan word, indien dit klinies aangedui word.

Aanvullende terapie moet oorweeg word vir die voorkoming van maniese episodes, omdat doeltreffendheid van LAMICTIN in manie nog nie oortuigend bevestig is nie.

Aanbevole dosisverhoging na die totale daaglikse stabilisering-onderhoudsdosis vir volwassenes (ouer as 18 jaar) wat vir BIPOLÊRE SIEKTE behandel word:

Behandelings-regimen	**Weke 1 - 2**	**Weke 3 - 4**	**Week 5**	**Teiken Stabiliserings-dosis (Week 6)****
a) Aanvullende terapie met ensieminhibeerders, bv. valproaat	12,5 mg (wat as 25 mg op alternatiewe dae gegee word)	25 mg (een keer per dag)	50 mg (een keer per dag of twee verdeelde dosisse)	100 mg (een keer per dag of twee verdeelde dosisse) (maksimum daaglikse dosis van 200 mg)
b) Aanvullende terapie met ensieminduseerders, bv. karbamasepien en fenobarbitoon in pasiënte wat NIE valproaat neem NIE	50 mg (een keer per dag)	100 mg (twee verdeelde dosisse)	200 mg (twee verdeelde dosisse)	300 mg in week 6, wat tot 400 mg/dag indien nodig in week 7 verhoog word (twee verdeelde dosisse)
c) Aanvullende terapie met geneesmiddels wat geen bekende kliniese farmakokinetiese interaksie met lamotrigien het nie, bv. litium, bupropioon OF monoterapie met lamotrigien	25 mg (een keer per dag)	50 mg (een keer per dag of twee verdeelde dosisse)	100 mg (een keer per dag of twee verdeelde dosisse)	200 mg (reikwydte 100-400 mg) (een keer per dag of twee verdeelde dosisse)

LET WEL: By pasiënte wat AEGs neem waar die farmakokinetiese interaksie met LAMICTIN teenswoordig nie bekend is nie, moet die dosisverhoging soos aanbeveel vir LAMICTIN met gelyktydige valproaat, gebruik word.
** Die teiken stabiliseringsdosis sal verander afhangende van die kliniese respons.

a) **Aanvullende terapie met ensieminhibeerders, bv. valproaat:** By pasiënte wat gelyktydig ensiem-inhiberende geneesmiddels soos valproaat neem, is die aanvanklike dosis LAMICTIN 25 mg op alternatiewe dae vir 2 weke, gevolg deur 25 mg een keer per dag vir 2 weke. Die dosis behoort na 50 mg een keer per dag (of in twee verdeelde dosisse) in week 5 verhoog te word. Die gebruiklike teikendosis om optimale respons te bereik is 100 mg/dag wat een keer per dag of in twee verdeelde dosisse gegee word. Die dosis kan egter tot ’n maksimum daaglikse dosis van 200 mg, afhangende van kliniese respons, verhoog word.

b) Aanvullende terapie met ensieminduseerders, bv. karbamasepien en fenobarbitoon in pasiënte wat NIE valproaat neem NIE: In pasiënte wat ensiem-induserende geneesmiddels soos karbamasepien of fenobarbitoon neem en NIE valproaat neem NIE, is die aanvanklike dosis LAMICTIN 50 mg een keer per dag vir 2 weke, gevolg deur 100 mg/dag wat in twee verdeelde dosisse vir 2 weke gegee word. Die dosis behoort na 200 mg/dag, wat as twee verdeelde dosisse gegee word, in week 5 verhoog te word. Die dosis kan in week 6 tot 300 mg/dag verhoog word, maar die gebruiklike teikendosis om optimale respons te bereik is 400 mg/dag wat in twee verdeelde dosisse vanaf week 7 gegee kan word.

c) Aanvullende terapie met geneesmiddels wat geen kliniese farmakokinetiese interaksie met lamotrigien het nie, bv. litium, bupropioon, OF monoterapie met LAMICTIN: Die aanvanklike dosis LAMICTIN in pasiënte wat geneesmiddels met geen bekende/teoretiese farmakokinetiese interaksie saam met lamotrigien neem, of in monoterapie, is 25 mg een keer per dag vir 2 weke, gevolg deur 50 mg een keer per dag (of in twee verdeelde dosisse) vir 2 weke. Die dosis behoort na 100 mg/dag in week 5 verhoog te word. Die gebruiklike teikendosis om optimale respons te bereik is

200 mg/dag wat een keer per dag of as twee verdeelde dosisse gegee word. ’n Reikwydte van 100-400 mg is egter in kliniese studies gebruik.

Sodra die teiken daaglikse stabilisering-onderhoudsdosis bereik is, kan ander psigotropiese medikasies onttrek word soos in die doseringskedule hierna verduidelik (sien onderstaande tabel).

Totale daaglikse stabilisering-onderhoudsdosis in BIPOLÊRE SIEKTE na onttrekking van gelyktydige psigotropiese of anti-epileptiese geneesmiddels:

Behandelings-regimen	Week 1	Week 2	Week 3 en daarna*
a) Na onttrekking van ensiem-inhibeerders, bv. valproaat	Verdubbel die stabiliseringsdosis, maar moenie 100 mg/week oorskry nie d.i. die 100 mg/dag teiken stabiliserings-dosis sal in week 1 na 200 mg/dag verhoog word	Onderhou hierdie dosis (200 mg/dag) (twee verdeelde dosisse)	
b) Na onttrekking van ensieminduseerders, bv. karbamasepien, afhangende van die oorspronklike dosis	400 mg	300 mg	200 mg
	300 mg	225 mg	150 mg
	200 mg	150 mg	100 mg
c) Na onttrekking van ander psigotropiese of AEG geneesmiddels met geen bekende kliniese farmakokinetiese interaksie met lamotrigien, bv. litium, bupropioon	Onderhou teikendosis wat met dosisverhoging bereik is (200 mg/dag) (twee verdeelde dosisse) (reikwydte 100-400 mg)		
LET WEL: By pasiënte wat AEGs neem waar die farmakokinetiese interaksie met LAMICTIN teenswoordig nie bekend is nie, moet die dosisverhoging soos aanbeveel vir LAMICTIN met gelyktydige valproaat, gebruik word.			
* Die dosis kan indien nodig tot 400 mg/dag verhoog word.			

a) **Na onttrekking van aanvullende terapie met ensiem-inhibeerders, bv. valproaat:**

Die dosis van LAMICTIN behoort tot dubbel die oorspronklike teiken stabiliseringsdosis verhoog te word en dan op hierdie vlak onderhou word, nadat valproaat gestaak is.

b) **Na onttrekking van aanvullende terapie met ensiem-induseerders, bv. karbamasepien afhangende van die oorspronklike onderhoudsdosis**: Die dosis van LAMICTIN behoort geleidelik verminder te word oor 3 weke soos die ensiem-induseerder onttrek word.

c) **Na onttrekking van aanvullende terapie met ander psigotropiese of anti-epileptiese geneesmiddels met geen bekende kliniese farmakokinetiese interaksie met lamotrigien, bv. litium, bupropioon:** Die teikendosis wat in die dosisverhogingsprogram bereik is, behoort dwarsdeur die onttrekking van die ander medikasie onderhou te word.

Aanpassing van daaglikse LAMICTIN-dosering in pasiënte met BIPOLÊRE SIEKTE na byvoeging van ander medikasies:

Daar is geen kliniese ondervinding met die aanpassing van die daaglikse LAMICTIN-dosis na die byvoeging van ander medikasies nie. Die volgende aanbevelings gegrond op geneesmiddelinteraksiestudies, kan egter gemaak word (sien hierna).

Aanpassing van daaglikse LAMICTIN dosering in pasiënte met BIPOLÊRE SIEKTE na byvoeging van ander medikasies:

<table>
<tr><th>Behandelings-regimen</th><th>Huidige lamotrigien stabiliserings-dosis (mg/dag)</th><th>Week 1</th><th>Week 2</th><th>Week 3 en daarna</th></tr>
<tr><td rowspan="3">a) Byvoeging van ensieminhibeerders, bv. valproaat, afhangende van die oorspronklike dosis van LAMICTIN</td><td>200 mg</td><td>100 mg</td><td colspan="2">Onderhou hierdie dosis (100 mg/dag)</td></tr>
<tr><td>300 mg</td><td>150 mg</td><td colspan="2">Onderhou hierdie dosis (150 mg/dag)</td></tr>
<tr><td>400 mg</td><td>200 mg</td><td colspan="2">Onderhou hierdie dosis (200 mg/dag)</td></tr>
<tr><td rowspan="3">b) Byvoeging van ensieminduseerders, bv. karbamasepien in pasiënte wat NIE valproaat neem NIE en afhangende van die oorspronklike dosis van LAMICTIN</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>150 mg</td><td>150 mg</td><td>225 mg</td><td>300 mg</td></tr>
<tr><td>100 mg</td><td>100 mg</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>c) Byvoeging van ander psigotropiese of AEG geneesmiddels met geen bekende kliniese farmakokinetiese interaksie met lamotrigien, bv. litium, bupropioon</td><td colspan="4">Onderhou teikendosis wat met dosisverhoging bereik is (200 mg/dag) (reikwydte 100-400 mg)</td></tr>
<tr><td colspan="5">LET WEL: By pasiënte wat AEGs neem waar die farmakokinetiese interaksie met LAMICTIN teenswoordig nie bekend is nie, moet die dosisverhoging soos aanbeveel vir LAMICTIN met gelyktydige valproaat, gebruik word.</td></tr>
</table>

Staking van LAMICTIN in pasiënte met bipolêre siekte: Geen toename in die voorkoms, erns of soort nadelige ondervindings na skielike staking van LAMICTIN vergeleke met plasebo, het in kliniese studies voorgekom nie. Pasiënte mag dus LAMICTIN sonder ’n trapsgewyse vermindering van dosis staak.

Kinders (jonger as 18 jaar): Die veiligheid en doeltreffendheid van LAMICTIN in bipolêre siekte is nie in hierdie ouderdomsgroep geëvalueer nie. ’n Dosisaanbeveling kan dus nie gemaak word nie.

Algemene Doseringsaanbevelings vir LAMICTIN in Spesiale Pasiëntbevolkings:

Vrouens wat hormonale voorbehoedmiddels neem:

(a) ***Instelling van LAMICTIN in pasiënte wat alreeds hormonale voorbehoedmiddels neem:*** Alhoewel daar aangedui kon word dat ’n mondelikse voorbehoedmiddel die opruiming van lamotrigien verhoog het (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS en INTERAKSIES), behoort geen aanpassings van die aanbevole dosisverhogingsriglyne vir LAMICTIN alleenlik gegrond op die gebruik van hormonale voorbehoedmiddels nodig te wees nie. Dosisverhoging behoort die aanbevole riglyne te volg, wat gegrond is op die feit of LAMICTIN by ’n inhibeerder van lamotrigienglukuronidasie, bv. valproaat, bygevoeg word; of dat LAMICTIN by ’n induseerder van lamotrigienglukuronidasie bygevoeg word, bv. karbamasepien, fenitoïen, fenobarbital, primidoon of rifampisien; of dat LAMICTIN in die afwesigheid van valproaat, karbamasepien, fenitoïen, fenobarbital, primidoon of rifampisien, bygevoeg word (sien Tabel 1).

(b) **Instelling van hormonale voorbehoedmiddels in pasiënte wat alreeds onderhoudsdosisse van LAMICTIN neem en NIE induseerders van lamotrigienglukuronidasie neem NIE**: Dit mag nodig wees om die onderhoudsdosis van LAMICTIN tot tweevoudig te verhoog volgens die individuele kliniese respons (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS & INTERAKSIES).

(c) **Staking van hormonale voorbehoedmiddels in pasiënte wat alreeds onderhoudsdosisse van LAMICTIN neem en NIE induseerders van lamotrigienglukuronidasie neem NIE:** Dit mag nodig wees om die onderhoudsdosis van LAMICTIN tot so veel as 50 % te verlaag volgens die individuele kliniese respons

(sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS & INTERAKSIES).

Bejaardes (ouer as 65 jaar): Geen dosisaanpassing met betrekking tot die aanbevole skedule word benodig nie. Die farmakokinetika van lamotrigien in hierdie ouderdomsgroep verskil nie beduidend van die nie-bejaarde volwasse bevolking nie.

Lewerinkorting: Aanvanklike, verhogings- en onderhoudsdosisse moet gewoonlik met ongeveer 50 % verlaag word in pasiënte met matige (Child-Pugh graad B), en met 75 % in ernstige (Child-Pugh graad C) lewerinkorting. Verhogings- en onderhoudsdosisse moet volgens kliniese respons aangepas word.

Nierinkorting: Omsigtigheid moet uitgeoefen word wanneer LAMICTIN aan pasiënte met nierversaking toegedien word. Vir pasiënte met endstadium nierversaking moet die aanvanklike dosisse van LAMICTIN op die pasiënte se AEG-regimen gebaseer word; verminderde onderhoudsdosisse moet vir pasiënte met beduidende renale funksionele inkorting gebruik word.

NEWE-EFFEKTE:

Gegrond op die data wat tans beskikbaar is, is die ongewenste effekte in epilepsie- en bipolêr-spesifieke afdelings verdeel. Beide afdelings behoort egter geraadpleeg te word wanneer die algehele veiligheidsprofiel van LAMICTIN oorweeg word. Die volgende konvensie is vir die klassifisering van ongewenste effekte gebruik: Baie algemeen (≥1/10), algemeen (≥ 1/100, < 1/10), ongewoon (≥ 1/1 000, < 1/100), seldsaam (≥ 1/10 000, < 1/1 000), baie seldsaam (< 1/10 000).

Epilepsie:

Versteurings van die vel en onderhuidse weefsels:

Tydens kliniese monoterapie-studies:

Baie algemeen: veluitslag

Tydens ander kliniese ondervinding:

Baie algemeen: veluitslag

Seldsaam: Stevens-Johnson-sindroom

Baie seldsaam: toksiese epidermale nekrolise

In dubbel-blind, byvoeging kliniese studies, het veluitslae voorgekom in so veel as 10 % van pasiënte wat LAMICTIN geneem het en in 5 % van pasiënte wat plasebo geneem het. Die veluitslae het tot onttrekking van LAMICTIN in 2 % van pasiënte gelei. Die veluitslag, gewoonlik makulopapulêr in voorkoms, begin meestal binne 8 weke na aanvang van behandeling en verdwyn met onttrekking van LAMICTIN (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Ernstige, potensieel lewensbedreigende veluitslae, insluitend angio-edeem, Stevens-Johnson-sindroom en toksiese epidermale nekrolise is aangemeld. Alhoewel die meerderheid na geneesmiddelonttrekking herstel, ondervind sommige pasiënte onomkeerbare letselvorming en seldsame gevalle van geassosieerde sterftes het voorgekom (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Dit wil voorkom dat die algehele risiko van veluitslag sterk geassosieer word met hoë aanvangsdosisse LAMICTIN en oorskryding van die aanbevole dosisverhoging van LAMICTIN-terapie (sien DOSIS EN GEBRUIKSAANWYSINGS).

Veluitslag is ook al aangemeld as deel van ’n hipersensitiwiteitsindroom geassosieer met ’n wisselende patroon van sistemiese simptome (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Versteurings van die bloed- en limfatiese sisteem:

Baie seldsaam: hematologiese abnormaliteite, insluitend anemie, neutropenie, leukopenie, trombositopenie, pansitopenie, aplastiese anemie, agranulositose

Hematologiese abnormaliteite mag of mag nie met ’n hipersensitiwiteitsindroom geassosieer word (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Versteurings van die immuunsisteem:

Baie seldsaam: hipersensitiwiteitsindroom* (insluitend sulke simptome soos koors, limfadenopatie, edeem van die gesig, abnormaliteite van die bloed en lewer, gedissemineerde intravaskulêre koagulasie, veelvoudige orgaanversaking)

* Veluitslag is ook al aangemeld as deel van ’n hipersensitiwiteitsindroom geassosieer met ’n wisselende patroon van sistemiese simptome insluitend koors, limfadenopatie, edeem van die gesig, en abnormaliteite van die bloed en lewer. Die sindroom toon ’n wye spektrum van kliniese erns en mag in seldsame gevalle lei tot gedissemineerde intravaskulêre koagulasie en veelvoudige orgaanversaking. Dit is belangrik om op te let dat die vroeë tekens van hipersensitiwiteit (bv. koors, limfadenopatie) teenwoordig mag wees selfs al is die veluitslag nie waarneembaar nie. Indien sulke tekens en simptome teenwoordig is, moet die pasiënt onmiddellik geëvalueer, en LAMICTIN onttrek word indien geen alternatiewe etiologie gevind kan word nie (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

Psigiatriese versteurings:

Algemeen: prikkelbaarheid

Ongewoon: aggressie

Baie seldsaam: spiertrekking, hallusinasies, verwarring

Versteurings van die senusisteem:

Tydens kliniese monoterapie-studies:

Baie algemeen: hoofpyn

Algemeen: slaperigheid, slaaploosheid, duiseligheid, tremor, vertigo, parestesie

Ongewoon: ataksie

Tydens ander kliniese ondervinding:

Baie algemeen: hoofpyn, duiseligheid

Algemeen: nistagmus, tremor, ataksie, slaperigheid, slaaploosheid

Baie seldsaam: agitasie, wankelrigheid, verergering van Parkinson se siekte, ekstrapiramidale effekte, choreoatetose, toename in die frekwensie van konvulsies

Berigte is ontvang dat LAMICTIN simptome van Parkinsonisme in pasiënte met voorafbestaande Parkinson se siekte mag vererger en geïsoleerde berigte van ekstrapiramidale effekte en choreoatetose in pasiënte, sonder hierdie onderliggende toestand, is ook ontvang.

Oogversteurings:

Baie algemeen: diplopie, versteurde visie

Seldsaam: konjunktivitis

Gastroïntestinale versteurings:

Tydens kliniese monoterapie-studies:

Algemeen: naarheid

Tydens ander kliniese ondervinding:

Algemeen: gastroïntestinale versteuring (insluitend braking en diaree)

Hepatobiliêre versteurings:

Baie seldsaam: verhoogde lewerfunksietoetse, hepatiese disfunksie, hepatiese versaking

Hepatiese disfunksie kom gewoonlik in assosiasie met hipersensitiwiteitsreaksies voor, maar geïsoleerde gevalle is ook sonder duidelike tekens van hipersensitiwiteit aangemeld.

Muskuloskeletale en bindweefselversteurings:

Baie seldsaam: Lupus-agtige reaksies

Algemene versteurings en toestande by die toedieningsplek:

Algemeen: moegheid

Bipolêre Siekte:

Die onderstaande ongewenste effekte moet saam met dié wat in epilepsie waargeneem word, vir ’n algehele veiligheidsprofiel van LAMICTIN oorweeg word.

Versteurings van die vel en onderhuidse weefsels:

Tydens kliniese studies van bipolêre siekte:

Baie algemeen: veluitslag

Seldsaam: Stevens-Johnson-sindroom

Wanneer alle studies van bipolêre siekte (beheer en onbeheer) wat met LAMICTIN uitgevoer is oorweeg word, het veluitslae in 14 % van pasiënte op LAMICTIN voorgekom. In beheerde kliniese studies met bipolêre siekte pasiënte het veluitslae egter voorgekom in 9 % van pasiënte wat LAMICTIN, en in 8 % van pasiënte wat plasebo geneem het.

Versteurings van die senusisteem:

Tydens kliniese studies van bipolêre siekte:

Baie algemeen: hoofpyn

Algemeen: agitasie, slaperigheid, duiseligheid

Muskuloskeletale en bindweefselversteurings:

Tydens kliniese studies van bipolêre siekte:

Algemeen: artralgie

Algemene versteurings en toestande by die toedieningsplek:

Tydens kliniese studies van bipolêre siekte:

Algemeen: pyn, rugpyn

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Simptome en tekens: Akute inname van dosisse wat 10-20 keer hoër as die maksimum terapeutiese dosis was, is al gerapporteer. Oordosering het simptome insluitend nistagmus, ataksie, bewussyninkorting, en koma veroorsaak.

Behandeling: Indien oordosering sou voorkom, moet die pasiënt by ’n hospitaal opgeneem word en geskikte ondersteunende terapie ontvang. Indien toepaslik, moet maagspoeling toegepas word.

IDENTIFIKASIE:

LAMICTIN 25: Ligte gelerige-bruin, super-elliptiese tablet met meervoudige fasette, ongekeep, gemerk 'GSEC7' op een kant en '25' op die ander kant.

LAMICTIN 50: Ligte gelerige-bruin, super-elliptiese tablet met meervoudige fasette, ongekeep, gemerk 'GSEE1' op een kant en '50' op die ander kant.

LAMICTIN 100: Ligte gelerige-bruin, super-elliptiese tablet met meervoudige fasette, ongekeep, gemerk 'GSEE5' op een kant en '100' op die ander kant.

LAMICTIN 200: Ligte gelerige-bruin, super-elliptiese tablet met meervoudige fasette, ongekeep, gemerk 'GSEE7' op een kant en '200' op die ander kant.

LAMICTIN P2: Ondeursigtige, wit tot naaswit ronde tablette met ’n braambessie-geur. Een kant is afgeplat en gegraveer met LTG bokant die getal 2. Die ander kant is gegraveer met twee oorvleuelde super-ellipse wat reghoekig ten opsigte van mekaar geplaas is.

LAMICTIN P5: Wit tot naaswit met ’n braambessie-geur. Langwerpige, bikonvekse tablette, mag gekeep wees. Gemerk 'GS CL2' op die een kant en '5' op die ander kant. Die tablette mag effens gestippeld wees.

LAMICTIN P25: Wit tot naaswit met ’n braambessie-geur. Meervoudige fasette, super-ellipties, ongekeep. Gemerk 'GSCL5' op die een kant en '25' op die ander kant. Die tablette mag effens gestippeld wees.

LAMICTIN P50: Wit tot naaswit met ’n braambessie-geur. Meervoudige fasette, super-ellipties, ongekeep. Gemerk 'GSCX7' op een kant en '50' op die ander kant. Die tablette mag effens gestippeld wees.

LAMICTIN P100: Wit tot naaswit met ’n braambessie-geur. Meervoudige fasette, super-ellipties, ongekeep. Gemerk 'GSCL7' op een kant en '100' op die ander kant. Die tablette mag effens gestippeld wees.

LAMICTIN P200: Wit tot naaswit met ’n braambessie-geur. Meervoudige fasette, super-ellipties, ongekeep. Gemerk 'GSEC5' op een kant en '200' op die ander kant. Die tablette mag effens gestippeld wees.

AANBIEDING:

LAMICTIN 25: Stolpverpakking van 60 tablette.

LAMICTIN 50: Stolpverpakking van 60 tablette.

LAMICTIN 100:Stolpverpakking van 60 tablette.

LAMICTIN 200:Stolpverpakking van 60 tablette.

LAMICTIN P2: Wit plastiekbottel, met ’n peutervrye seël wat 30 tablette bevat.

LAMICTIN P5: Amber glasbottel wat 100 tablette bevat.

LAMICTIN P25: Amber glasbottel wat 60 tablette bevat.

LAMICTIN P50: Amber glasbottel wat 60 tablette bevat.

LAMICTIN P100: Amber glasbottel wat 60 tablette bevat.

LAMICTIN P200: Amber glasbottel wat 60 tablette bevat.

BERGINGSAANWYSINGS:

LAMICTIN Tablette (nie-dispergeerbaar):

Bewaar benede 30 ºC.

Hou droog.

Hou buite bereik van kinders.

LAMICTIN Dispergeerbare Tablette:

Beskerm teen lig.

Bewaar benede 30 ºC.

Hou droog.

Hou buite bereik van kinders.

REGISTRASIENOMMER:

LAMICTIN 25: Z/2.5/280

LAMICTIN 50: Z/2.5/281

LAMICTIN 100: Z/2.5/282

LAMICTIN 200: 29/2.5/0472

LAMICTIN P2: 36/2.5/0407

LAMICTIN P5: 29/2.5/0303

LAMICTIN P25: 29/2.5/0304

LAMICTIN P50: 32/2.5/0459

LAMICTIN P100: 29/2.5/0305

LAMICTIN P200: 32/2.5/0460

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:

GlaxoSmithKline South Africa (Edms) Bpk

Hawkinslaan 39

Epping Industrie 1, 7460

DATUM VAN PUBLIKASIE VAN DIE VOUBILJET:

10 Augustus 2007