SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE:

LAMICTIN 25, 50, 100 and 200 Tablets

LAMICTIN P2, P5, P25 and P50 Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each LAMICTIN 25 tablet contains: 25 mg lamotrigine.

Contains sugar (lactose monohydrate, 24,7 mg/tablet).

Each LAMICTIN 50 tablet contains: 50 mg lamotrigine.

Contains sugar (lactose monohydrate, 49,4 mg/tablet).

Each LAMICTIN 100 tablet contains: 100 mg lamotrigine.

Contains sugar (lactose monohydrate, 98,8 mg/tablet).

Each LAMICTIN 200 tablet contains: 200 mg lamotrigine.

Contains sugar (lactose monohydrate, 114,7 mg/tablet).

For full list of excipients, see Section 6.1

Each LAMICTIN P2 dispersible tablet contains: 2 mg lamotrigine

Contains sweetener (saccharin sodium (0,4 mg/tablet))

Each LAMICTIN P5 dispersible tablet contains: 5 mg lamotrigine

Contains sweetener (saccharin sodium (1,0 mg/tablet))

Each LAMICTIN P25 dispersible tablet contains: 25 mg lamotrigine

Contains sweetener (saccharin sodium (0,625 mg/tablet))

Each LAMICTIN P50 dispersible tablet contains: 50 mg lamotrigine

Contains sweetener (saccharin sodium (1,25 mg/tablet))

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

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 above 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, unscored. 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.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

EPILEPSY:

Adults and adolescents (over 12 years of age):

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 anti-epileptic 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.

4.2 Posology and method of administration:

Posology:

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 section 4.4).

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 should be 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 section 4.4). 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 section 5.2), 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 anti-epileptic medicines are withdrawn to achieve LAMICTIN monotherapy or other anti-epileptic drugs (AEDs)/medicines are added-on to treatment regimes containing LAMICTIN, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

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 should be equal to the lower number of whole tablets.

Dosage in epilepsy monotherapy:

Adults and adolescents (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 adolescents (over 12 years of age):

In those patients taking concomitant antiepileptic drugs (AEDs) or other medications (see section 4.5) 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 two weeks, followed by 25 mg once a day for two 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 2 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 and adolescents 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 section 4.5).	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 section 4.5), 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 section 4.4).

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 should be equal to the lower number of whole tablets.

In those patients taking concomitant AEDs or other medications (see section 4.5) that induce lamotrigine glucorindation 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 bodymass/day for 2 weeks. Thereafter, the dose should be increased by a maximum of 1,2 mg/kg bodymass every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg bodymass/day given once a day or 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 bodymass/day given once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,3 mg/kg bodymass every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg bodymass/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 lamotrigine dose is 0,3 mg/kg bodymass/day given once a day or in two divided doses for 2 weeks, followed by 0,6 mg/kg bodymass/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 bodymass every 1-2 weeks until an optimal response is achieved, or 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 section 4.5).	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 one to two 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 section 4.5**),** 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. DO NOT attempt to give partial quantities of the LAMICTIN dispersible tablets. ** If the calculated dose of LAMICTIN cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet.				

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see section 4.4).

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:

LAMICTIN has not been studied as monotherapy in children less than 2 years of age or as add-on therapy in children less than 1 month of age. The safety and efficacy of LAMICTIN as add-on therapy of partial seizures in children aged 1 month to 2 years has not been established. Therefore, LAMICTIN is not recommended in children less than 2 years of age.

BIPOLAR DISORDER:

Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

The following transition regimen should be followed**.** The transition regimen involves escalating the dose of LAMICTIN to a maintenance stabilisation dose over six weeks (see Table 3) after which other psychotropic and/or anti-epileptic medicines can be withdrawn, if clinically indicated (see Table 4).

Table 3: 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 inhibitors of lamotrigine glucuronidation 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 inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or, with other inducers of lamotrigine glucuronidation (see section 4.5)	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) Monotherapy with LAMICTIN OR Adjunctive therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see section 4.5)	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 inhibitors of lamotrigine glucuronidation e.g., valproate:

In patients taking glucuronidation 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 inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate. This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other medicines known to induce lamotrigine glucuronidation, including liponavir/ritonavir (see section 4.5):**

In those patients currently taking medicines that induce lamotrigine glucuronidation 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) **Monotherapy with lamotrigine OR Adjunctive therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see section 4.5):**

The initial LAMICTIN dose is 25 mg once a day for two 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 4).

Table 4: Maintenance stabilisation total daily dose in BIPOLAR DISORDER following withdrawal of concomitant psychotropic or anti-epileptic medicines

Treatment Regimen	Week 1	Week 2	Week 3 onwards*

a)	**Following withdrawal of inhibitors of lamotrigine glucuronidation e.g., valproate**	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	Maintain this dose (200 mg/day) (two divided doses)
b)	**Following withdrawal of inducers of lamotrigine glucuronidation depending on original dose.** This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or, with other inducers of lamotrigine glucuronidation (see section 4.5)	400 mg	300 mg / 200 mg
		300 mg	225 mg / 150 mg
		200 mg	150 mg / 100 mg
c)	Following withdrawal of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100-400 mg)	
NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMICTIN is currently not known, the treatment regimen as recommended for LAMICTIN is to initially maintain the current dose and adjust the LAMICTIN treatment based on clinical response.			
* Dose may be increased to 400 mg/day as needed			

a) **Following withdrawal of adjunct therapy with inhibitors of lamotrigine glucuronidation 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 inducers of lamotrigine glucuronidation, depending on original maintenance dose. This regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone or other medicines known to induce lamotrigine glucuronidation (see section 4.5):**

The dose of LAMICTIN should be gradually reduced over 3 weeks as the glucuronidation inducer is withdrawn.

c) **Following withdrawal of adjunct therapy with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):**
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 Table 5):

Table 5: Adjustment of LAMICTIN daily dosing in patients with BIPOLAR DISORDER following the addition of other medications

Treatment Regimen	Current lamotrigine Stabilisation dose (mg/day)	Week 1	Week 2	Week 3 onwards
a) Addition of lamotrigine glucuronidation inhibitors e.g., valproate, depending on original dose of LAMICTIN	200 mg	100 mg	Maintain this dose (100 mg/day)	
	300 mg	150 mg	Maintain this dose (150 mg/day)	
	400 mg	200 mg	Maintain this dose (200 mg/day)	
b) Addition of lamotrigine glucuronidation inducers in patients NOT taking valproate and depending on original dose of LAMICTIN. This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primodone Or with other inducers of lamotrigine glucuronidation	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
c) Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMICTIN is currently not known, the treatment regimen as recommended for LAMICTIN with concurrent valproate, should be used.				

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 stepwise reduction of dose.

Children and adolescents (less than 18 years of age):

LAMICTIN is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (see section 4.4). 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 section 4.4 and 4.5), 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 valproate (an inhibitor of lamotrigine glucuronidation) or to an inducer of lamotrigine glucuronidation, or whether LAMICTIN is added in the absence of valproate or an inducer of lamotrigine glucuronidation (see Table 1 for epilepsy and Table 3 for bipolar patients).

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

The maintenance dose of LAMICTIN will in most cases need to be increased by as much as two-fold (see section 4.4 & 4.5).

It is recommended that from the time that the hormonal contraceptive is started, the LAMICTIN dose is increased by 50-100 mg/day every week, according to the individual

clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases.

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

The maintenance dose of LAMICTIN will in most cases need to be decreased by as much as 50 % (see section 4.4 & 4.5). It is recommended to gradually decrease the daily dose of LAMICTIN by 50-100 mg each week (at a rate not exceeding 25 % of the total daily dose per week) over a period of 3 weeks unless the clinical response indicates otherwise.

Use with atazanavir/ritonavir:

Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (see section 4.5), no adjustments to the recommended dose escalation guidelines for LAMICTIN should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether LAMICTIN is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether LAMICTIN is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

In patients already taking maintenance doses of LAMICTIN and not taking glucuronidation inducers, the LAMICTIN dose may need to be increased if atazanavir/ritonavir is added or decreased if atazanavir/ritonavir is discontinued.

Elderly (over 65 years of age):

No dosage adjustment from recommended schedule is required. The pharmacokintetics 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.

4.3 Contraindications:

LAMICTIN is contraindicated in individuals with known hypersensitivity to lamotrigine.

4.4 Special warnings and precautions for use:

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 medical practitioner 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 lamotrigine may provoke rebound seizures, in patients with epilepsy. 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 that a therapeutic dose is maintained in children, 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 should be equal to the lower number of whole tablets (see section 4.2).

Skin Reactions:

There have been reports of adverse skin reactions, which have predominantly 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 (SJS) and toxic epidermal necrolysis have been reported especially in children and in patients (adults and children) who also used valproate (see section 4.8). Cases have however 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 withdrawal of LAMICTIN, some patients experience irreversible scarring and there have been cases of associated death.

In adults enrolled in studies utilising the current LAMICTIN dosing recommendations, the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as SJS (1 in 1000).

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 clinical trials with LAMICTIN in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000.

In children, the initial presentation of a rash can be mistaken for an infection; medical practitioners should consider the possibility of a 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 section 4.2).
- Concomitant use of valproate, which increases the mean half-life of LAMICTIN nearly two-fold (see section 5.2 and 4.2).

Caution is also required when treating patients with a history of allergy or rash to other anti-epileptic medicines, as the frequency of non-serious rash after treatment with LAMICTIN was approximately three times higher in these patients than in those without such history.

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 related to LAMICTIN treatment. 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, pruritis, facial oedema, abnormalities of the blood, liver, and kidney, aseptic meningitis 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.
Aseptic meningitis was reversible on withdrawal of the LAMICTIN in most cases but recurred in a number of cases on re-exposure to LAMICTIN. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. LAMICTIN should not be restarted in patients who have discontinued due to aseptic meningitis associated with treatment of LAMICTIN.

Haemophagocytic lymphohistiocytosis (HLH):

HLH has occurred in patients taking LAMICTIN (see section 4.8). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. LAMICTIN should be discontinued unless an alternative aetiology can be established.

Clinical worsening and suicide risk:

There is evidence that patients with bipolar disorder and with epilepsy, have an elevated risk for suicidality. This risk may continue during treatment.

Suicidal ideation and behaviour have been reported in patients treated with AEDs, including LAMICTIN in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEDs (including LAMICTIN) has also shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours. Patients (and caregivers of patients) should be advised to seek medical advice, should signs of suicidal ideation or behaviour emerge.

Patients receiving LAMICTIN for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing LAMICTIN, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 section 4.5). Following titration, higher maintenance doses of LAMICTIN (by as much as two-fold) will be needed in most cases 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 section 4.2 'General Dosing Recommendations for LAMICTIN in Special Patient Populations'.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during LAMICTIN therapy and LAMICTIN dosing adjustments will be needed in most cases.

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 lamotrigine 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 section 4.5). 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.

Effect of LAMICTIN on organic cationic transporter 2 (OCT 2) substrates: Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (see section 4.5). This may result in increased plasma levels of certain medicines that are substantially excreted via this route. Co-administration of LAMICTIN with OCT 2 substrates with a narrow therapeutic index e.g., dofetilide is not recommended.

Dihydrofolate reductase: 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 haemoglobin concentration, mean corpuscular volume, serum or red blood cell folate concentrations.

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.

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

Cardiac rhythm and conduction abnormalities: *In vitro* testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these *in vitro*

findings, lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia in patients with clinically important structural or functional heart disease. Therefore, any expected or observed benefit of lamotrigine for those patients must be carefully weighed against the potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia (see section 5.1).

Bipolar Disorder:

***Children and adolescents (less than 18 years of age)*:**

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. LAMICTIN should not be used in children and adolescents with bipolar disorder.

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. Patients with rare hereditary problems of galactose intolerance, e.g., galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take LAMICTIN tablets (see section 2).

4.5 Interaction with other medicines and other forms of interaction:

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicines that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs,

may also enhance the metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

Those medicines that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in the table below. Specific dosing guidance for these medicines is provided in section 4.2. In addition, this table lists those medicines which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such medicines would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Effects of medicines on the concentration of lamotrigine:

Medicines that increase the concentration of lamotrigine (doubling of lamotrigine half-life)	**Medicines that decrease the concentration of lamotrigine (halving lamotrigine half-life)**	**Medicines have little or no that effect on the concentration of lamotrigine**
Valproate	Atazanavir/ritonavir	Aripiprazole
	Carbamazepine	
	Ethinyloestradiol/levonorgestrel combination	Bupropion
	Phenytoin	Felbamate
	Phenobarbitone	Gabapentin
	Phenytoin	Oxcarbazepine
	Primidone	
	Rifampicin	Lacosamide
		Levetiracetam
		Lithium
		Olanzapine
		Oxcarbazepine
		Paracetamol
		Perampanel
		Topiramate

Medicines that increase the concentration of lamotrigine (doubling of lamotrigine half-life)	Medicines that decrease the concentration of lamotrigine (halving lamotrigine half-life)	Medicines have little or no that effect on the concentration of lamotrigine
		Pregabalin Zonisamide
For dosing guidance, see section 4.2 - General Dosing Recommendations for LAMICTIN in Special Patient Populations, plus for women taking hormonal contraceptives also see section 4.4 – Hormonal Contraceptives.		

Interactions involving AEDs (see section 4.2):

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 AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, 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 lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

In a study in healthy adult volunteers using doses of 200 mg lamotrigine and 1200 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).

In a study of healthy volunteers, co-administration of felbamate (1 200 mg twice daily) with LAMICTIN (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Based on a retrospective analysis of plasma levels in patients who received LAMICTIN both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate

that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of LAMICTIN resulted in a 15 % increase in topiramate concentrations.

In a study of patients with epilepsy, co-administration of zonisamide (200 to 400 mg/day) with LAMICTIN (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10 %.

Although increases in the plasma concentrations of other anti-epileptic medicines have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant anti-epileptic medicines. Evidence from *in vitro* studies indicates that lamotrigine does not displace other anti-epileptic medicines from protein binding sites.

Interactions involving other psychotropic 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 lamotrigine.

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 a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C_{max} of lamotrigine by an average of 24 % and 20 %, respectively. LAMICTIN at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of LAMICTIN 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with LAMICTIN, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone and none when LAMICTIN was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of LAMICTIN (≥ 100 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7-day period and continued once daily for a further 7 days. An average reduction of approximately 10 % in C_{max} and AUC of lamotrigine was observed.

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 medicines 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 (see section 4.2 – General Dosing Recommendations for LAMICTIN in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives) and Special warnings and precautions for use).

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 section 4.4). 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, menstrual disorders, amenorrhoea have been reported. Any change in the menstrual bleeding patterns should be reported to the physician of the patient.

Interactions involving other medicines:

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 section 4.2).

In a study in healthy volunteers, lopinavir/ritonavir approximately halved the plasma concentrations of lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the treatment regimen recommended for LAMICTIN and concurrent glucuronidation inducers should be used (see section 4.2).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single 100 mg dose) by an average of 32 % and 6 %, respectively (see section 4.2 - General Dosing Recommendations for LAMICTIN in Special Patient Populations).

In a study in healthy adult volunteers, paracetamol 1 g (four times daily) reduced the plasma AUC and C_{min} of lamotrigine by an average of 20 % and 25 %, respectively.

Data from *in vitro* assessment of the effect of lamotrigine at OCT 2 demonstrate that lamotrigine, but not the N (2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with IC_{50} values of 53,8 µM (see section 4.4).

Interactions involving laboratory tests:

Lamotrigine has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for phencyclidine (PCP). A more specific alternative chemical method should be used to confirm a positive result.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

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

Use during pregnancy:

There is some evidence of an increased risk of oral cleft malformations following exposure to LAMICTIN in pregnancy.

The decision to use LAMICTIN during pregnancy should be taken by the physician following assessment of the benefit / risk profile.

A large amount of data on pregnant women exposed to LAMICTIN monotherapy during the first trimester of pregnancy (more than 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts. Animal studies have shown developmental toxicity (see section 5.3).

If therapy with LAMICTIN is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels. Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels during pregnancy with a potential risk of loss of seizure control. After birth, lamotrigine levels may increase rapidly with a risk of dose-related adverse events. Therefore, lamotrigine serum concentrations should be monitored before, during and after pregnancy, as well as shortly after birth. If necessary, the dose should be adapted to maintain the lamotrigine serum concentration at the same level as before pregnancy or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Breastfeeding:

The decision to breastfeed should be taken in by the mother in consultation with the physician. The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50 % of the mothers'. Therefore, in some breastfed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

4.7 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.

4.8 Undesirable 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:

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 lamotrigine (see section 4.4).

Serious, potentially life-threatening skin rashes, including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Although the majority recover on withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

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 section 4.2).

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see section 4.4).

Blood and lymphatic system disorders:

Very rare: haematological abnormalities (including, anaemia, neutropenia, leukopenia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocystosis), lymphadenopathy

Haematological abnormalities and lymphadenopathy may or may not be associated with a DRESS/Hypersensitivity Syndrome (see section 4.4 Immune system disorders*).

Immune system disorders:

Very rare: DRESS/hypersensitivity syndrome* including such symptoms as, fever, lymphadenopathy, facial oedema, abnormailities of the blood, liver, and kidney,

*Rash has also been reported as part of a hypersensitivity syndrome which 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 section 4.4).

Psychiatric disorders:

Common: aggression, irritability

Very rare: tics, hallucinations, confusion

Nervous system disorders:

Very common: headache

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

Uncommon: ataxia

Rare**:** nystagmus.

Eye disorders:

Uncommon**:** diplopia, blurred vision.

Gastrointestinal disorders:

Common: nausea**,** vomiting, diarrhoea.

Hepato-biliary 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:

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 12 % of patients on LAMICTIN. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8 % of patients taking LAMICTIN and in 6 % of patients taking placebo.

Nervous system disorders:

Very Common: headache

Common: agitation, somnolence, dizziness.

Musculoskeletal and connective tissue disorders:

Common: arthralgia.

General disorders and administration site conditions:

Common: pain, back pain.

Post-marketing Data:

Blood and lymphatic system disorders: *haemophagocytic* lymphohistiocytosis (see section 4.4).

Immune system disorders: hypogammaglobulinaemia

Skin and subcutaneous disorders: alopecia

Psychiatric disorders: nightmares

Nervous system disorders: somnolence, headache, ataxia, dizziness, nystagmus, tremor, insomnia, aseptic meningitis (see section 4.4), agitation, unsteadiness, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, and in epilepsy only, increase in seizure frequency.

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

Eye disorders: conjunctivitis

Renal and Urinary disorders: Tubulointerstitial nephritis*

* may occur in association with uveitis.

Reporting of side effects:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

Symptoms and signs: Ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported, including fatal cases. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has also been observed in overdose patients (see section 4.8).

Treatment: In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 2.5 Anti-epileptics

In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia.

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.

5.2 Pharmacokinetic properties:

In healthy fasting young adult volunteers, lamotrigine is 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 decreased by concomitant medication with a mean value of approximately 14 hours when given with enzyme-inducing medicines such as carbamazepine and phenytoin and increased to a mean of approximately 70 hours when co-administered with sodium

valproate alone (see section 4.2). 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 medicines 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 section 4.2).

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 clinically 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: 12 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' AED regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see section 4.2).

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 section 4.2).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

LAMICTIN tablet:

Microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycollate, magnesium stearate and iron oxide yellow (E172).

LAMICTIN dispersible tablet:

Calcium carbonate, low substituted hydroxypropyl cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone, saccharin sodium, blackcurrant flavour and magnesium stearate.

6.2 Incompatibilities:

N/A

6.3 Shelf life:

Tablets: 25, 50, 100, 200: 36 months

Dispersible:

P2: 24 months

P5, P25, P50: 36 months

6.4 Special precautions for storage:

LAMICTIN Tablets (non-dispersible):

Store at or below 30 ºC.

Keep dry.

LAMICTIN Dispersible Tablets:

Protect from light.

Store at or below 30 ºC.

Keep dry.

6.5 Nature and contents of container:

Lamictin tablets are packed into:

- PVC-PVdC/aluminium foil blister packs of 60 tablets, or
- PVC blisters with aluminium foil lidding blisters of 56 tablets or
- Child-resistant PVC/aluminium paper lidding blisters of 56 tablets.

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

LAMICTIN P5 tablets are packed into:

- Amber glass bottle containing 100 tablets, or

- PVC-PVdC/aluminium foil blister packs containing 100 tablets, or
- White HDPE bottles with a child resistant/tamper evident closure containing 60 tablets.

LAMICTIN P25 tablets are packed into:

- Amber glass bottle containing 60 tablets, or
- PVC/PVdC/aluminium foil blister packs containing 60 tablets.

LAMICTIN P50: Amber glass bottle containing 60 tablets.

6.6 Special precautions for disposal:

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

LAMICTIN 25 :	Z/2.5/280	LAMICTIN P2:	36/2.5/0407
LAMICTIN 50 :	Z/2.5/281	LAMICTIN P5:	29/2.5/0303
LAMICTIN 100 :	Z/2.5/282	LAMICTIN P25:	29/2.5/0304
LAMICTIN 200:	29/2.5/0472	LAMICTIN P50:	32/2.5/0459

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Registration date:

LAMICTIN 25, LAMICTIN 50, LAMICTIN 100: 20 January 1994

LAMICTIN 200: 19 September 1995

LAMICTIN P2: 28 May 2004

LAMICTIN P5: 23 February 1995

Lamictin P25: 28 February 1995

LAMICTIN P50: 10 October 2000

10. DATE OF REVISION OF THE TEXT:

26 September 2022

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