LAMICTAL

Lamotrigine

QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMICTAL Tablets:
Each film-coated tablet contains 25, 50 and 100 mg lamotrigine.

LAMICTAL Dispersible/Chewable Tablets:
Each tablet contains 2 and 5 mg lamotrigine, which may be chewed, dispersed in a liquid or swallowed whole.

PHARMACEUTICAL FORM

Tablets.

Dispersible/chewable tablets.

CLINICAL PARTICULARS

Indications

EPILEPSY

- **Adults (over 12 years of age)**

LAMICTAL is indicated for use as adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

- **Children (2 to 12 years of age)**

LAMICTAL is indicated as adjunctive therapy in the treatment of epilepsy, for partial seizures and generalised seizures including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended.

After epileptic control has been achieved during adjunctive therapy, concomitant anti-epileptic drugs (AEDs) may be withdrawn and patients continued on *LAMICTAL* monotherapy.

BIPOLAR DISORDER

- **Adults (18 years of age and over)**

LAMICTAL is indicated for the prevention of depressive episodes in patients with bipolar disorder. Safety and efficacy of *LAMICTAL* in the acute treatment of mood episodes has not been established. The physician who elects to use *LAMICTAL* for periods extending beyond 18 months should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Dosage and Administration

LAMICTAL tablets should be swallowed whole, and should not be chewed or crushed.

LAMICTAL dispersible/chewable tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

If a calculated dose of *LAMICTAL*, e.g. for use in children (epilepsy only) or patients with hepatic impairment, cannot be divided into multiple lower strength tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

It is strongly recommended that therapy with lamotrigine is initiated at the recommended doses. Careful incremental titration of the dose may decrease the severity of skin rashes. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by co-administration of *LAMICTAL* with valproate. However, cases have been reported in the absences of these factors. Therefore, it is important that the dosing recommendations be followed closely.

Restarting Therapy

Prescribers should assess the need for escalation to maintenance dose when restarting *LAMICTAL* in patients who have discontinued *LAMICTAL* for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for *LAMICTAL* (see *Warnings and 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 *LAMICTAL* exceeds five half-lives (see *Pharmacokinetics*), *LAMICTAL* should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that *LAMICTAL* not be restarted in patients who have discontinued due to rash associated with prior treatment with *LAMICTAL* unless the potential benefit clearly outweighs the risk.

EPILEPSY

When concomitant anti-epileptic drugs are withdrawn to achieve *LAMICTAL* monotherapy or other AEDs are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see *Interactions*).

- **Adults (over 12 years of age) (see Table 1)**

Dosage in Epilepsy Monotherapy

The initial *LAMICTAL* dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of *LAMICTAL* to achieve the desired response.

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see *Warnings and Precautions*).

Dosage in Epilepsy Add-On Therapy

In patients taking valproate with/without any other AED, the initial *LAMICTAL* 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 to 50 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or in two divided doses.

In those patients taking concomitant AEDs or other medications (see *Interactions*) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial *LAMICTAL* dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks.

Thereafter, the dose should be increased by a maximum of 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 to 400 mg/day given in two divided doses.

Some patients have required 700 mg/day of *LAMICTAL* to achieve the desired response.

In those patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see *Interactions*), the initial *LAMICTAL* dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Table 1: Recommended treatment regimen in EPILEPSY 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 one to two weeks
Add-on therapy with valproate regardless of any concomitant medications		12.5 mg (given 25 mg 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 one to two 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 one to two weeks
	This dosage regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see *Interactions*)	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 one to two weeks
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see *Interactions*), the treatment regimen as recommended for *LAMICTAL* with concurrent valproate should be used.				

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see *Warnings and Precautions*).

- **Children (2 to 12 years of age) (see Table 2)**

In patients taking valproate with/without any other AED, the initial *LAMICTAL* dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 5 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

In those patients taking concomitant AEDs or other medications (see *Interactions*) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial *LAMICTAL* dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5 to 15 mg/kg/day given once a day or in two divided doses, with a maximum of 400 mg/day.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

Table 2: Recommended treatment regimen in EPILEPSY for children aged 2-12 years (total daily dose in mg/kg bodyweight/day) on combined drug therapy

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 one to two 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 one to two 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.

In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see *Interactions*), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.
*Where 2 mg tablets are the lowest marketed strength: If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then *LAMICTAL* should not be administered. *Where 5 mg tablets are the lowest marketed strength: if the calculated daily dose in patients taking valproate is 2.5 to 5 mg, then 5 mg may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 2.5 mg, then *LAMICTAL* should not be administered. It is not possible to accurately initiate therapy using the recommended dosing guidelines in paediatric patients weighing less than 17 kg.

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see *Warnings and Precautions*).

It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.

- **Children aged less than 2 years**

Lamotrigine 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 lamotrigine as add-on therapy of partial seizures in children aged 1 month to 2 years has not been established (see *Clinical Studies*). Therefore, *LAMICTAL* is not recommended in children less than 2 years of age.

BIPOLAR DISORDER

- **Adults (18 years of age and over)**

Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see *Warnings and Precautions*).

LAMICTAL 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 *LAMICTAL* to a maintenance stabilisation dose over six weeks (see Table 3) after which other psychotropic and/or anti-epileptic drugs can be withdrawn, if clinically indicated (see Table 4).

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with *LAMICTAL* in mania has not been conclusively established. There is no evidence of an increased risk of mania, hypomania or mixed type episodes with lamotrigine treatment compared to placebo.

Table 3: Recommended dose escalation to the maintenance total daily stabilisation dose for adults (18 years of age and over) 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 *Interactions*)**	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 *LAMICTAL* **OR** **Adjunctive therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see *Interactions*)**	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200 mg (range 100 – 400mg) (once a day or two divided doses)
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for *LAMICTAL* 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 *LAMICTAL* dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two 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 drugs known to induce lamotrigine glucuronidation (see *Interactions*)
In those patients currently taking drugs that induce lamotrigine glucuronidation and NOT taking valproate, the initial *LAMICTAL* dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two 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 *LAMICTAL* OR adjunctive therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see *Interactions*)
The initial *LAMICTAL* dose is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two 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 to 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 adults (18 years of age and over) with BIPOLAR DISORDER following withdrawal of concomitant psychotropic or anti-epileptic drugs

<table>
<tr><th>Treatment Regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td>(a) Following withdrawal of inhibitors of lamotrigine glucuronidation 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 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 Interactions)</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>(c) Following withdrawal of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)</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="4">NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen recommended for LAMICTAL is to initially maintain the current dose and adjust the LAMICTAL treatment based on clinical response.</td></tr>
</table>

*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 *LAMICTAL* 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 drugs known to induce *LAMICTAL* glucuronidation (see *Interactions*).
The dose of *LAMICTAL* should be gradually reduced over three 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 *Interactions*).
The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

Adjustment of *LAMICTAL* daily dosing in patients with BIPOLAR DISORDER following addition of other medications

There is no clinical experience in adjusting the *LAMICTAL* daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (see Table 5 below):

Table 5: Adjustment of *LAMICTAL* daily dosing in adults (18 years of age and over) with BIPOLAR DISORDER following the addition of other medications

<table>
<tr><th>Treatment Regimen</th><th>Current LAMICTAL Stabilisation Dose (mg/day)</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards</th></tr>
<tr><td rowspan="3">(a) Addition of inhibitors of lamotrigine glucuronidation e.g. Valproate, depending on original dose of LAMICTAL</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) Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate and depending on original dose of LAMICTAL. This dosage regimen should be used with:

Phenytoin
Carbamazepine
Phenobarbitone
Primidone

Or with other inducers of lamotrigine glucuronidation (see Interactions)</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) Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day)

(range 100 - 400 mg)</td></tr>
<tr><td colspan="5">NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen as recommended for LAMICTAL with concurrent valproate, should be used.</td></tr>
</table>

Discontinuation of *LAMICTAL* in adult patients with BIPOLAR DISORDER

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

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

LAMICTAL is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (see *Warnings and Precautions*). Safety and efficacy of *LAMICTAL* in bipolar disorder has not been established in this age group. Therefore, a dosage recommendation cannot be made.

GENERAL DOSING RECOMMENDATIONS FOR *LAMICTAL* IN SPECIAL PATIENT POPULATIONS

- **Women taking hormonal contraceptives**

(a) Starting *LAMICTAL* in patients already taking hormonal contraceptives:

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see *Warnings and Precautions* & *Interactions*), no adjustments to the recommended dose escalation guidelines for *LAMICTAL* should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether lamotrigine is added to an inhibitor of lamotrigine glucuronidation e.g. valproate; whether *LAMICTAL* is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone, rifampin or lopinavir/ritonavir; or whether *LAMICTAL* is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone, rifampicin or lopinavir/ritonavir (see Table 1 for epilepsy and Table 3 for bipolar disorder patients).

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

The maintenance dose of *LAMICTAL* will in most cases need to be increased by as much as two-fold (see *Warnings and Precautions* & *Interactions*). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 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 *LAMICTAL* and NOT taking inducers of lamotrigine glucuronidation:

The maintenance dose of *LAMICTAL* will in most cases need to be decreased by as much as 50% (see *Warnings and Precautions* & *Interactions*). It is recommended to gradually decrease the daily dose of lamotrigine by 50 to 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.

- **Elderly (over 65 years of age)**

No dosage adjustment from recommended schedule is required. The pharmacokinetics of *LAMICTAL* in this age group do not differ significantly from a non-elderly adult population. As older patients are more likely to suffer from intercurrent illness and require medications to treat other medical conditions, lamotrigine should be used cautiously in these patients and they should be monitored regularly.

- **Hepatic impairment**

Initial, escalation 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 (see *Pharmacokinetics*).

- **Renal impairment**

Caution should be exercised when administering *LAMICTAL* to patients with renal failure. For patients with end-stage renal failure, initial doses of *LAMICTAL* should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (see *Warnings and Precautions*). For more detailed pharmacokinetic information (see *Pharmacokinetics*).

Contraindications

LAMICTAL tablets and dispersible/chewable tablets are contraindicated in individuals with known hypersensitivity to lamotrigine or any other ingredient of the preparation.

Warnings and Precautions

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of *LAMICTAL* treatment. The majority of rashes are mild and self-limiting; however serious rashes requiring hospitalisation and discontinuation of *LAMICTAL* have also been reported. These have included potentially life-threatening rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see *Adverse Reactions*). It is not possible to predict reliably which rashes will prove to be life-threatening. Accordingly, *LAMICTAL* should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related.

Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

In adults enrolled in studies utilising the current *LAMICTAL* 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).

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

The risk of serious skin rashes in children is higher than in adults.

Available data from a number of studies suggest the incidence of rashes associated with 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 *LAMICTAL* and exceeding the recommended dose escalation of *LAMICTAL* therapy (see *Dosage and Administration*)
- concomitant use of valproate (see *Dosage and Administration*)

Caution is also required when treating patients with a history of allergy or rash to other anti-epileptic drugs as it was found in two studies (n=767 and n=988) on the frequency of rash after treatment with lamotrigine that the rate of rash was approximately three to four times higher in patients with such history, than without.

All patients (adults and children) who develop a rash should be promptly evaluated and *LAMICTAL* withdrawn immediately unless the rash is clearly not drug related. It is recommended that *LAMICTAL* not be restarted in patients who have discontinued due to rash associated with prior treatment with *LAMICTAL* unless the potential benefit clearly outweighs the risk.

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney and aseptic meningitis (see *Adverse Reactions*). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) 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 *LAMICTAL* discontinued if an alternative aetiology cannot be established.

Aseptic Meningitis

Therapy with *LAMICTAL* increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate.

Post-marketing cases of aseptic meningitis have been reported in paediatric and adult patients taking *LAMICTAL* for various indications. Symptoms upon presentation have included headache, fever, nausea, vomiting and nuchal rigidity. Rash, photophobia, myalgia, chills, altered consciousness and somnolence were also noted in some cases. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment. In most cases, symptoms were reported to resolve after discontinuation of *LAMICTAL*. Re-exposure resulted in a rapid return of symptoms (from 30 minutes to 1 day following re-initiation of treatment) that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Some of the patients treated with *LAMICTAL* who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.

Cerebrospinal fluid (CSF) analysed at the time of clinical presentation in reported cases was characterised by a mild to moderate pleocytosis, normal glucose levels and mild to moderate increase in protein. CSF white blood cell count differentials showed a predominance of neutrophils in a majority of the cases, although a predominance of lymphocytes was reported in approximately one-third of the cases. Some patients also had new onset of signs and symptoms of involvement of other organs (predominantly hepatic and renal involvement), which may suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has occurred in patients taking *LAMICTAL* (see *Adverse Reactions*). 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. *LAMICTAL* should be discontinued unless an alternative aetiology can be established.

Suicide risk

Symptoms of depression and/or bipolar disorder may occur in patients with epilepsy, and there is evidence that patients with epilepsy and bipolar disorder have an elevated risk for suicidality.

Twenty-five to 50% of patients with bipolar disorder attempt suicide at least once, and may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including *LAMICTAL*.

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

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.

Clinical worsening in bipolar disorder

Patients receiving *LAMICTAL* 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 the medication, 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 *LAMICTAL* efficacy:

An ethinylestradiol/levonorgestrel (30 micrograms/150 micrograms) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see *Interactions*). Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. In women not already taking an inducer of lamotrigine 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 lamotrigine dose increases are made in the days before or during the week of inactive medication. For dosing instructions, see "*General Dosing Recommendations for LAMICTAL in Special Patient Populations, Dosage and Administration*".

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

Effects of other hormonal contraceptive preparations or HRT on *LAMICTAL*:

Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of *LAMICTAL* on hormonal contraceptive efficacy:

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinylestradiol/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, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with *LAMICTAL* cannot be excluded. A limited number of reports have been received of unexpected pregnancies and of menstrual bleeding disorders (e.g. breakthrough bleeding) occurring with the concomitant use of *LAMICTAL* and hormonal contraceptives. Therefore, patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding while receiving *LAMICTAL* in combination with these medications.

Effect of lamotrigine on organic cationic transporter 2 (OCT 2) substrates

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (see *Interactions*). This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Co-administration of *LAMICTAL* with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

Acute Multi-organ Failure

Multi-organ failure, which in some cases has been fatal or irreversible, has been observed in patients receiving *LAMICTAL*. Fatalities associated with multi-organ failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 paediatric patients who received *LAMICTAL* in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multi-organ failure have also been reported in compassionate plea and post-marketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial cause.

Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multi-organ dysfunction and disseminated intravascular coagulation 9 to

14 days after *LAMICTAL* was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both paediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with *LAMICTAL* was discontinued.

Binding in the Eye and Other Melanin-Containing Tissues

Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Dihydrofolate reductase

Lamotrigine 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, *LAMICTAL* did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal Failure

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

Patients taking other preparations containing lamotrigine

LAMICTAL tablets and dispersible/chewable tablets should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

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 *LAMICTAL* in patients with Brugada syndrome.

EPILEPSY

As with other AEDs, abrupt withdrawal of *LAMICTAL* may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of *LAMICTAL* should be gradually decreased over a period of two weeks.

There are reports in the literature that severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of *LAMICTAL*.

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.

Interactions

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs 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 drugs that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in Table 6. Specific dosing guidance for these drugs is provided in *Dosage and Administration*. In addition, this table lists those drugs which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such drugs 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.

Table 6: Effects of drugs on the concentration of lamotrigine

Drugs that increase the concentration of lamotrigine	Drugs that decrease the concentration of lamotrigine	Drugs that have little or no effect on the concentration of lamotrigine
Valproate	Atazanavir/ritonavir Carbamazepine	Aripiprazole Bupropion

	Ethinylestradiol / levonorgestrel combination Lopinavir/ritonavir Phenobarbitone Phenytoin Primidone Rifampicin	Felbamate Gabapentin Lacosamide Levetiracetam Lithium Olanzapine Oxcarbazepine Paracetamol Perampanel Pregabalin Topiramate Zonisamide

For dosing guidance, see *Dosage and Administration — General Dosing Recommendations for LAMICTAL in Special Patient Populations*, plus for women taking hormonal contraceptives also see *Warnings and Precautions – Hormonal Contraceptives.*

- **Interactions involving AEDs (see *Dosage and Administration*)**

Valproate, which inhibits the glucuronidation of lamotrigine, 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, enhance the metabolism of lamotrigine. Other drug classes which induce hepatic drug-metabolising enzymes may also enhance the metabolism of lamotrigine.

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 *LAMICTAL*. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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. The pharmacokinetic interaction between lamotrigine and oxcarbazepine in children has not been studied.

In a study of healthy volunteers, co-administration of felbamate (1200 mg twice daily) with *LAMICTAL* (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 *LAMICTAL* both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential drug 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 *LAMICTAL* 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 *LAMICTAL* (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 lacosamine (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 changes in the plasma concentrations of other anti-epileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant anti-epileptic drugs. Evidence from *in vitro* studies indicates that lamotrigine does not displace other anti-epileptic drugs from protein binding sites.

- **Interactions involving other psychoactive agents (see *Dosage and Administration*)**

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 *LAMICTAL*.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of *LAMICTAL* 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. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of *LAMICTAL* 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 lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when *LAMICTAL* was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (>/=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 drugs 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 micrograms ethinylestradiol/150 micrograms 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 *Dosage and Administration - General Dosing Recommendations for LAMICTAL in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives)* and *Warnings and Precautions – Hormonal Contraceptives*.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylestradiol 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 estradiol 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 and Precautions*). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

- **Interactions involving other medications**

In a study in 10 male volunteers, 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 lamotrigine and concurrent glucuronidation inducers should be used (see *Dosage and Administration*).

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 lamotrigine and concurrent glucuronidation inducers should be used (see *Dosage and Administration*).

In a study in healthy adult volunteers, paracetamol 1g (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 an IC_{50} value of 53.8 µM (see *Warnings and Precautions*).

- **Interactions involving laboratory tests**

LAMICTAL 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.

Pregnancy and Lactation

Fertility

Administration of lamotrigine did not impair fertility in animal reproductive studies. There is no experience of the effect of *LAMICTAL* on human fertility.

Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 8,700 women exposed to *LAMICTAL* monotherapy during the first trimester of pregnancy. These data do not exclude an increased risk for major congenital malformations. Although a number of registries have reported an increase in the risk of isolated oral cleft malformations, a completed case control study with 259 exposures to lamotrigine therapy did not demonstrate an increased risk of oral clefts compared to other

major congenital malformations following exposure to lamotrigine (see Pre-clinical Safety Data). Animal studies have shown developmental toxicity.

The data on use of *LAMICTAL* in polytherapy combinations are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant *LAMICTAL* use.

As with other medicines, *LAMICTAL* should only be used during pregnancy if the expected benefits outweigh the potential risks.

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 *LAMICTAL* therapy should be ensured.

Lactation

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 mother's. Therefore, in some breastfed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.

Effects on Ability to Drive and Use Machines

Two volunteer studies have demonstrated that the effect of *LAMICTAL* on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with *LAMICTAL*, adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how *LAMICTAL* therapy affects them before driving or operating machinery.

Epilepsy

As there is individual variation in response to all anti-epileptic drug therapy, patients should consult their physician on the specific issues of driving and epilepsy.

Adverse Reactions

The adverse reactions identified from epilepsy or bipolar disorder clinical trial data have been divided into indication specific sections. Additional adverse reactions identified through post-marketing surveillance for both indications are included in the post-marketing section. All three sections should be consulted when considering the overall safety profile of *LAMICTAL*.

The following convention has been utilised for the classification of undesirable effects: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000).

EPILEPSY

The following adverse reactions were identified during epilepsy clinical trials and should be considered alongside those seen in the bipolar disorder clinical trials and post-marketing sections for an overall safety profile of *LAMICTAL*.

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 in adults, skin rashes occurred in up to 10% of patients taking *LAMICTAL* and in 5% of patients taking placebo. The skin rashes led to the withdrawal of *LAMICTAL* treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of *LAMICTAL* (see *Warnings and Precautions*).

Rarely, serious potentially life-threatening skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) 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 Precautions*).

The overall risk of rash appears to be strongly associated with:

- high initial doses of *LAMICTAL* and exceeding the recommended dose escalation of *LAMICTAL* therapy (see *Dosage and Administration*)
- concomitant use of valproate (see *Dosage and Administration*)

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms (see *Warnings and Precautions* and *Immune system disorders***).

Blood and lymphatic system disorders

Very rare:	Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis)
Frequency not known:	Lymphadenopathy

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

Immune system disorders

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

**Rash has also been reported as part of this syndrome which shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) 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 *LAMICTAL* discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common:	Aggression, irritability
Very rare:	Tics, hallucinations, confusion

Nervous system disorders

Very common:	Headache
Common:	Somnolence, insomnia, dizziness, tremor
Uncommon:	Ataxia
Rare:	Nystagmus

Eye disorders

Uncommon:	Diplopia, blurred vision

Gastrointestinal disorders

Common:	Nausea, vomiting, 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 following adverse reactions were identified during bipolar disorder clinical trials and should be considered alongside those seen in the epilepsy clinical trials and post-marketing sections for an overall safety profile of *LAMICTAL*.

Skin and subcutaneous tissue disorders

Very common: Skin rash
Rare: Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with *LAMICTAL* are considered, skin rashes occurred in 12% of patients on *LAMICTAL*. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking *LAMICTAL* 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:

This section includes adverse reactions identified through post-marketing surveillance for both indications. These adverse reactions should be considered alongside those seen in the epilepsy and bipolar disorder clinical trials sections for an overall safety profile of *LAMICTAL*.

Blood and lymphatic system disorders

Very rare: Haemophagocytic lymphohistiocytosis (see *Warnings and Precautions*)

Immune system disorders

Very rare: Hypogammaglobulinaemia

Skin and subcutaneous tissue disorders

Rare: Alopecia

Psychiatric disorders

Very rare: Nightmares

Nervous system disorders

Very common:	Somnolence, ataxia, headache, dizziness
Common:	Nystagmus, tremor, insomnia
Rare:	Aseptic meningitis (see *Warnings and Precautions*)
Very rare:	Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis

There have been reports that *LAMICTAL* 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

Very common:	Nausea, vomiting
Common:	Diarrhoea

Renal and urinary disorders

Very rare: Tubulointerstitial nephritis*

* may occur in association with uveitis

Epilepsy only

Nervous system disorders

Very rare: Increase in seizure frequency

Overdose

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose, have 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.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code: N 03 AX 09

Mechanism of Action

The results of pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage-gated sodium channels. It produces a use- and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

Pharmacodynamic Effects

In tests designed to evaluate the central nervous system effects of drugs, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor co-ordination and eye movements, increased body sway and produced subjective sedative effects.

In another study, single oral doses of 600 mg carbamazepine significantly impaired fine visual motor co-ordination and eye movements, while increasing both body sway and heart rate, whereas results with lamotrigine at doses of 150 mg and 300 mg did not differ from placebo.

Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g. in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Pharmacokinetics

Absorption

Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary.

Distribution

Binding to plasma proteins is about 55%; it is very unlikely that displacement from plasma proteins would result in toxicity.

The volume of distribution is 0.92 to 1.22 L/kg.

Metabolism

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine.

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination

The mean steady state clearance in healthy adults is 39 ± 14 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

The half-life of lamotrigine is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see *Dosage and Administration* and *Interactions*).

Special Patient Populations

- **Children**

Clearance adjusted for bodyweight is higher in children than in adults with the highest values in children under five 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 and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (see *Dosage and Administration*).

- **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**

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis 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 hours haemodialysis session. For this patient population, initial doses of *LAMICTAL* should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment.

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

Clinical Studies

Clinical efficacy and safety of adjunctive therapy in patients aged 1 to 24 months with partial seizures

The effectiveness of lamotrigine as adjunctive therapy in patients aged 1 to 24 months with partial seizures was evaluated in a multi-centre, double-blind, placebo-controlled add-on trial (Study LAM20006). Lamotrigine was added to 1 or 2 AEDs during an open-label phase (n=177).

Lamotrigine was given on alternate days or once daily if an initial total dose or dose-titration step of less than 2 mg was required. Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. If valproate was used as an AED, lamotrigine was added only after an infant had been on valproate for 6 months without liver function test abnormalities. The safety and efficacy of lamotrigine in patients weighing less than 6.7 kg, and taking valproate or AEDs other than carbamazepine, phenytoin, phenobarbital or primidone has not been evaluated.

Patients achieving a 40% or greater reduction in partial seizure frequency (n=38) were randomised to either gradual withdrawal to placebo (n=19) or continued lamotrigine (n=19) for up to 8 weeks. The primary efficacy endpoint was based on the difference in the proportion of subjects receiving lamotrigine or placebo who met defined escape criteria. The escape criteria allowed the withdrawal of subjects from the study if their epilepsy conditions showed any signs of clinical deterioration. Statistical significance on the primary endpoint was not achieved; however, fewer patients met escape criteria on lamotrigine (58%) compared with placebo (84%) and took a longer time to meet escape criteria (42 versus 22 days).

A total of 256 subjects between 1 to 24 months of age have been exposed to lamotrigine in the dose range 1 to 15 mg/kg/day for up to 72 weeks. The safety profile of lamotrigine in children aged 1 month to 2 years was similar to that in older children except that clinically significant worsening of seizures (>=50%) was reported more often in children under 2 years of age (26%) as compared to older children (14%).

Clinical efficacy in the prevention of depressive episodes in patients with bipolar disorder:

Adults (18 years of age and over)

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

Clinical study SCAB20003 was a multicentre, 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 *LAMICTAL* monotherapy or *LAMICTAL* plus psychotropic medication, patients were randomly assigned into one of five treatment groups: *LAMICTAL* (50, 200, 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/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 analysed 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 *LAMICTAL* 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.

Clinical study SCAB2006 was a multicentre, double-blind, double dummy, placebo and lithium-controlled, randomised, flexible dose evaluation of *LAMICTAL* in the long-term prevention of relapse and recurrence of mania and/or depression in patients with bipolar I disorder who had recently or were currently experiencing a manic or hypomanic episode. Once stabilised using *LAMICTAL* monotherapy or *LAMICTAL* plus psychotropic

medication, patients were randomly assigned into one of three treatment groups: *LAMICTAL* (100 to 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/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 analysed 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 0.023. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the *LAMICTAL* patients had longer times to first depressive episode than placebo 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 *LAMICTAL* therapy was not significantly different to placebo.

Pre-clinical Safety Data

Reproductive toxicology studies with lamotrigine in animals at doses less than the human dose of 400 mg/day [on a body surface area (mg/m^2) basis] showed developmental toxicity (increased mortality, decreased body weight, increased structural variations, neurobehavioral abnormalities), but no teratogenic effects. However, as lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

The results of a wide range of mutagenicity tests indicate that lamotrigine does not present a genetic risk to man.

Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablets:
Lactose
Microcrystalline cellulose
Povidone
Sodium starch glycolate
Iron oxide yellow (E172)
Magnesium stearate

Dispersible/Chewable Tablets:
Calcium carbonate
Low substituted hydroxypropyl cellulose
Aluminium magnesium silicate
Sodium starch glycolate

Povidone
Saccharin sodium
Blackcurrant flavour
Magnesium stearate

Incompatibilities

None reported.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store above 30°C. Keep dry.

Protect dispersible/chewable tablets from light.

Nature and Contents of Container

As registered locally.

Instructions for Use/Handling

None.

Not all presentations are available in every country.

Version number: GDS48/IPI25SI

Date of issue: 18 February 2020

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