HCP-MEPPO
Publishers of MEPPO and MODERN MEDICINE

LAMICTAL™
GlaxoSmithKline

Lamotrigine

QUALITATIVE AND QUANTITATIVE COMPOSITION
Tablets: LAMICTAL, 25, 50, 100 and 200 mg.

Dispersible/Chewable Tablets:
LAMICTAL, 2, 5, 25, 50, 100 and 200 mg.

PHARMACEUTICAL FORM
Tablets: film-coated, dispersible/chewable.

CLINICAL PARTICULARS
Indications
EPILEPSY
• Adults (over 12 years of age)
Lamotrigine is indicated for use as adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalized seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome.

• Children (2 to 12 years of age)
Lamotrigine 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After epileptic control has been achieved during adjunctive therapy, concomitant anti-epileptic drugs (AEDs) may be withdrawn and patients continued on LAMICTAL monotherapy.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 mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

Dosage and Administration
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.

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 antiepileptic 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.

See Table.

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

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

In patients taking AEDs where the pharmacokinetic interaction with *LAMICTAL* is currently not known (see Interactions), the treatment regimen as recommended for *LAMICTAL* with concurrent valproate should be used.

Table 2: Recommended treatment regimen in EPILEPSY for children aged 2-12 years (total daily dose in mg/kg body-weight/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.
	This dosage regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	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 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 lamotrigine 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.

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

*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 Lamictal therapy using the recommended dosing guidelines in paediatric patients weighing less than 17 kg.

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 in two divided doses, with a maximum of 400 mg/day.

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions), the initial LAMICTAL dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 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.

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

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.

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

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

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.

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).

(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, next page):

Discontinuation Of LAMICTAL 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 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 evaluated 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 and 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 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 may need to be increased by as much as two-fold according to the individual clinical response (see Warnings and Precautions & Interactions).

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

The maintenance dose of LAMICTAL may need to be decreased by as much as 50% according to the individual clinical response (see Warnings and Precautions & Interactions).

• 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.

• 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

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 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 100-400 mg) (once a day or two divided doses)

NOTE: In patients taking AEDs where the pharmacokinetic interaction with *LAMICTAL* 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.

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

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 Interactions*)	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 Interactions*)	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 *LAMICTAL* is currently not known, the treatment regimen as recommended for *LAMICTAL* with concurrent valproate, should be used.
* Dose may be increased to 400 mg/day as needed

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).

In adults enrolled in studies utilizing 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 epileptic 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). See Table.

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

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 a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver (see Adverse Reactions). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, 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.

Clinical worsening and suicide risk

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

Table 5: Adjustment of LAMICTAL daily dosing in patients with BIPOLAR DISORDER following the addition of other medications				
Treatment Regimen	**Current *LAMICTAL* Stabilisation dose (mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
(a) Addition of inhibitors of lamotrigine glucuronidation e.g. Valproate, depending on original dose of *LAMICTAL*	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 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)	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 Interactions*)	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with *LAMICTAL* is currently not known, the treatment regimen as recommended for *LAMICTAL* with concurrent valproate, should be used.				

emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including LAMICTAL. There is also evidence that patients with epilepsy have an elevated risk for suicidality.

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.

The incidence of suicidal ideation and behaviour was evaluated in a pooled analysis of placebo-controlled clinical trials with lamotrigine involving a total of 6467 patients from a number of indications.

In the subset of bipolar disorder trials, the rate of events was numerically, but not statistically significantly, greater for lamotrigine (29/1212 [2.4%]) compared with placebo (19/1054 [1.8%]). In a pooled analysis of psychiatric indications, events were more common in the first month of treatment, in patients taking lamotrigine. Behavioural events were more common in males.

In the subset of epilepsy trials, there were no statistically significant differences in the rate of events

between lamotrigine and placebo. Although the number of suicidal ideation and behaviour events was too low (6/1073 [0.6%] on lamotrigine and 2/805 [0.3%] on placebo) to allow a definitive comparison between treatment groups, the relative rate reported from this lamotrigine analysis is consistent with a possible class effect reported by the US Food and Drug Administration, based on their meta-analysis of 11 anticonvulsant drugs including lamotrigine.

Hormonal contraceptives

Effects of hormonal contraceptives on LAMICTAL efficacy:

An ethinyloestradiol/levonorgestrel (30 mcg / 150 mcg) 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) may be needed 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 may be needed.

Other oral contraceptive and 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 (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see Interactions). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with LAMICTAL cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, ie, breakthrough bleeding.

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.

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, multiorgan 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

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

Table 6: Effects of other drugs on glucuronidation of lamotrigine (*see Dosage and Administration*)

Drugs that significantly inhibit glucuronidation of lamotrigine	Drugs that significantly induce glucuronidation of lamotrigine	Drugs that do not significantly inhibit or induce glucuronidation of lamotrigine
Valproate	Carbamazepine	Lithium
	Phenytoin	Bupropion
	Primidone	Olanzapine
	Phenobarbitone	Oxcarbazepine
	Rifampicin	Felbamate
	Lopinavir/ritonavir	Gabapentin
	Ethinyloestradiol/ levonorgestrel combination*	Levetiracetam
		Pregabalin
		Topiramate
		Zonisamide

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

- **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 antiepileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the metabolism glucuronidation of lamotrigine and 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.

In a study of healthy volunteers, coadministration of felbamate (1,200 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, coadministration 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.

Although changes in the plasma concentrations of other antiepileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant antiepileptic drugs. Evidence from in vitro studies indicates that lamotrigine does not displace other antiepileptic drugs from protein binding sites.

• 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 Cmax of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. 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 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 mcg ethinyloestradiol/150 mcg 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 Cmax, 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 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 Cmax, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see Warnings 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).

Pregnancy and Lactation

Administration of lamotrigine did not impair fertility in animal reproductive studies.

There is no experience of the effect of LAMICTAL on human fertility.

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 2000 women exposed to LAMICTAL monotherapy during the first trimester of pregnancy. Whilst the data provide no evidence for a substantial increase in the overall risk of major birth malformations associated with LAMICTAL use, one registry has reported an increase in the risk of isolated oral cleft malformations. This increased risk has not been confirmed in a pooled analysis of the data from six other registries. 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.

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

The potential benefits of breast feeding 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 co-ordination, 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 antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

Adverse Reactions

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 LAMICTAL.

The following convention has been utilised for the classification of undesirable effects:

very common:	≥1 in 10
common:	≥1 in 100 and <1 in 10
uncommon:	≥1 in 1,000 and <1 in 100
rare:	≥1 in 10,000 and <1 in 1,000
very rare:	<1/10,000.

EPILEPSY

Skin and subcutaneous tissue disorders

During monotherapy clinical trials:

Very common: Skin rash.

During other clinical experience:

Very common: Skin rash.

Rare: Stevens Johnson syndrome.

Very rare: Toxic epidermal necrolysis.

In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking 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 a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see Immune system disorders**).

Blood and lymphatic system disorders

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

Haematological abnormalities may or may not be associated with the hypersensitivity syndrome (see Immune system disorders**).

Immune system disorders

Very rare: Hypersensitivity syndrome** (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation (DIC), multiorgan failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) 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 LAMICTAL discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common: Irritability.

Uncommon: Aggression.

Very rare: Tics, hallucinations, confusion.

Nervous system disorders

During monotherapy clinical trials:

Very common: Headache.

Common: Drowsiness, insomnia, dizziness, tremor.

Uncommon: Ataxia.

During other clinical experience:

Very common: Headache, dizziness.

Common: Nystagmus, tremor, ataxia, drowsiness, insomnia.

Very rare: Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

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

During monotherapy clinical trials:
Common: Nausea.

During other clinical experience:
Common: Gastrointestinal disturbance (including vomiting and 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 LAMICTAL.

Skin and subcutaneous tissue disorders
During bipolar disorder clinical trials:

Very Common:Skin rash.
Rare: Stevens Johnson syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with LAMICTAL are considered, skin rashes occurred in 14% of patients on LAMICTAL.

Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 9% of patients taking LAMICTAL and in 8% of patients taking placebo.

Nervous system disorders
During bipolar disorder clinical trials:
Very Common: Headache.
Common: Agitation, somnolence, dizziness.

Musculoskeletal and connective tissue disorders

During bipolar disorder clinical trials:
Common: Arthralgia.

General disorders and administration site conditions

During bipolar disorder clinical trials:
Common: Pain, back pain.

Overdose
Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

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.

Pharmacokinetics

Absorption

Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 h 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 h. 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 h when given with glucuronidation - inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 h 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 h when given with enzyme-inducing drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 h 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 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 hemodialysis), and 1.57 ml/min/kg (during hemodialysis) compared to 0.58 ml/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 h (chronic renal failure), 57.4 h (between hemodialysis) and 13.0 h (during hemodialysis), compared to 26.2 h 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 h hemodialysis 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 in the prevention of depressive episodes in patients with bipolar disorder:

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

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 analyzed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.003 to 0.029.

In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the 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 analyzed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.003 to 0.023.

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 in excess of the human therapeutic dosage showed 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 glycollate
Iron oxide yellow (E172)
Magnesium stearate.

Dispersible/Chewable Tablets:

Calcium carbonate
Low substituted hydroxypropyl cellulose
Aluminium magnesium silicate
Sodium starch glycollate
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 30oC. 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: GDS28/IPI07

Date of issue: 11 February 2008