Lamictal™ tablets and liquitabs

Lamotrigine

QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet of the preparation LAMICTAL contains 25 mg, 50 mg or 100 mg of Lamotrigine respectively.

One Liquitab of the preparation LAMICTAL contains 2 mg, 5 mg, 25 mg, 50 mg, 100 mg or 200 mg of Lamotrigine respectively.

PHARMACEUTICAL FORM

LAMICTAL tablets: light yellow tablets, square of rounded corners, of one surface multiplane, and the other one flat with an engraving: tablets 25 mg: "GSEC7" on one side and "25" on the other; tablets 50 mg: "GSEE1" on one side and "50" on the other; tablets 100 mg: "GSEE5" on one side and "100" on the other, respectively.

LAMICTAL Liquitabs 2 mg: round, white or almost white tablets; on one side the edges are cut aslant, with an engraving "LTG 2", on the other there are two ellipses engraved, which cross perpendicularly.

LAMICTAL Liquitabs 5 mg: white tablets, biconvex, oblong, with an engraving "GSCL2" on one side and "5" on the other.

LAMICTAL Liquitabs 25 mg, 50 mg, 100 mg and 200 mg: white tablets, square of rounded corners, of one surface multiplane and the other one flat, with an engraving: tablets 25 mg: "GSCL5" on one side and "25" on the other; tablets 50 mg: "GSCX7" on one side and "50" on the other; tablets 100 mg: "GSCL7" on one side and "100" on the other, tablets 200 mg: "GSEC5" on one side and "200" on the other.

CLINICAL PARTICULARS

Indications

EPILEPSY

Adults and children over 12 years of age

The preparation LAMICTAL is an antiepileptic drug used in monotherapy of:

• partial simple and complex seizures,

• generalized seizures (including tonic-clonic seizures with primary and secondary generalization).

Adults and children over 2 years of age

The preparation LAMICTAL is indicated in the combined treatment (with other antiepileptic drugs) of:

• partial simple and complex seizures,

• generalized seizures (including tonic-clonic seizures with primary and secondary generalization).

The preparation LAMICTAL is also indicated in the treatment of epileptic seizures related to the Lennox-Gastaut syndrome

Tablets containing 2 mg and 5 mg of lamotrigine are indicated solely in the treatment of epilepsy.

Initial monotherapy treatment in newly diagnosed paediatric patients from 2 to 12 years of age is not recommended.

BIPOLAR DISORDER

Adults (18 years of age and over)

LAMICTAL is indicated in the prophylaxis of bipolar affective disorders, especially in the prevention of depressive episodes recurrence.

Tablets containing 2 mg and 5 mg of lamotrigine are not indicated in the prophylaxis of bipolar affective disorders.

Dosage and Administration

LAMICTAL Tablets should be swallowed whole with a little water.

LAMICTAL liquitabs 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).

DOSAGE IN EPILEPSY MONOTHERAPY

Adults (over 12 years of age)

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 Precautions and Warnings).

It is not recommended to use monotherapy with the preparation LAMICTAL in newly diagnosed epilepsy in children from 2 to 12 years of age.

DOSAGE IN EPILEPSY ADD-ON THERAPY

Adults (over 12 years of age)

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 oxcarbazepine without any other inducers or inhibitors of lamotrigine glucuronidation, 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 on alternate days)	25 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25 – 50 mg every 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
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	25 mg (once a day)	50 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks
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, thereafter, the dose should be increased until optimal response is achieved.				

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

In patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, 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 body weight 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 body weight 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.

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.
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	0.3 mg/kg (once daily or in two divided doses)	0.6 mg/kg (once daily or in 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, thereafter, the dose should be increased until optimal response is achieved.				
*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. *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.				

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

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 Precautions and Warnings).

LAMICTAL is recommended in patients with bipolar affective disorders, with a risk of another depressive episode occurrence in the future.

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 antiepileptic 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.

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 on alternate days)	25 mg (once a day)	50 mg (once a day or on 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 lithium, bupropion, olanzapine, oxcarbazepine, or other agents known not to significantly induce or inhibit lamotrigine glucuronidation.	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 psychotropic drugs 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.

a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. 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).

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 given as two divided doses 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 lithium, bupropion, olanzapine, oxcarbazepine, or other agents known not to significantly induce or inhibit lamotrigine glucuronidation. 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 (once daily or in two divided doses). 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 BIPOLAR DISORDER following withdrawal of concomitant psychotropic or antiepileptic drugs

Treatment regimen	Week 1	Week 2	Week 3 onwards*
(a) Following withdrawal of inhibitors of lamotrigine glucuronidation e.g. Valproate	Double the dose which supports stabilisation, but by not more than 100 mg within a 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 psychotropic or AED drugs in patients not taking significant inducers or inhibitors of lamotrigine glucuronidation (including lithium salts, bupropion, olanzapine, oxcarbazepine)	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (Range 100-400 mg)		
NOTE: In patients taking psychotropic drugs 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

(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 psychotropic or antiepileptic drugs with no significant pharmacokinetic interaction with LAMICTAL e.g. lithium salts, bupropion, olanzapine, oxcarbazepine.

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 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 psychotropic or AED drugs with no significant pharmacokinetic interaction with LAMICTAL e.g. lithium salts, bupropion, olanzapine, oxcarbazepine	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
NOTE: In patients taking psychotropic drugs where the pharmacokinetic interaction with LAMICTAL is currently not known, the treatment regimen as recommended for LAMICTAL with concurrent valproate, should be used.				

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 (less than 18 years of age)

Safety and efficacy of LAMICTAL in bipolar disorder has not been evaluated in this age group. Therefore, LAMICTAL is not indicated in the treatment of bipolar affective disorders in children less than 18 years of age.

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 or rifampin; or whether LAMICTAL is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (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 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 severe renal disorders (see Warnings and Precautions). For more detailed pharmacokinetic information (see Pharmacokinetics).

Contraindications

LAMICTAL tablets and liquitabs 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).

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 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 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.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms 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.

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 lamotrigine.

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 lamotrigine 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 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 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.

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.

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 lamotrigine with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

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 liquitabs 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 P_{450} 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

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
	Ethinyloestradiol/ levonorgestrel combination*	Levetiracetam
	Lopinavir/ritonavir	Gabapentin
	Atazanavir/ritonavir	Pregabalin
	Ethinylestradiol/ levonorgestrel combination*	Topiramate
		Zonisamide
		Aripiprazole

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

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.

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.

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 lamotrigine (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 lamotrigine 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 lamotrigine resulted in a 15% increase in topiramate concentrations.

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

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. 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 lamotrigine 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 lamotrigine 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 Cmax and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

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 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.

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 C_{max}, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see Warnings 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.

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, 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 a more potent inhibitor of OCT 2 than cimetidine, with IC50 values of 53.8 μM and 186 μM, respectively.

Interactions involving laboratory tests

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

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. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although data from a limited number of registries have reported an increase in the risk of isolated oral cleft malformations. A case control study did not demonstrate an increased risk of oral clefts compared to other defects following exposure to lamotrigine. 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.

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 breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects 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. Adverse reactions identified through post-marketing surveillance are included in the Epilepsy section.

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

EPILEPSY

Skin and subcutaneous tissue disorders

Very common: Skin rash.
Rare: Stevens Johnson syndrome.
Very rare: Toxic epidermal necrolysis.

In double-blind, add-on clinical trials, 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 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, lymphadenopathy.

Haematological abnormalities and lymphadenopathy 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), multi-organ failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (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: Aggression, irritability.
Very rare: Tics, hallucinations, confusion.

Nervous system disorders

During monotherapy clinical trials:
Very common: Headache.
Common: Somnolence, insomnia, dizziness, tremor.
Uncommon: Ataxia.
Rare: Nystagmus.

During other clinical experience:
Very common: Somnolence, ataxia, headache, dizziness.
Common: Nystagmus, tremor, insomnia.
Rare: Aseptic meningitis.
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

During monotherapy clinical trials:
Uncommon: Diplopia, blurred vision.

During other clinical experience:
Very common: Diplopia, blurred vision.
Rare: Conjunctivitis.

Gastrointestinal disorders

During monotherapy clinical trials:
Common: Nausea, vomiting, diarrhoea.

During other clinical experience:
Very common: Nausea, vomiting.
Common: 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 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

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, 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.

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 P_{450} 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablets:

Lactose
Microcrystalline cellulose
Polyvidone
Sodium starch glycollate
Iron oxide yellow (E172)
Magnesium stearate.

Liquitabs:

Calcium carbonate
Low substituted hydroxypropyl cellulose
Aluminium magnesium silicate
Sodium starch glycollate
Povidone
Saccharin sodium
Blackcurrant flavour
Magnesium stearate

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Tablets 25 mg, 50 mg, 100 mg, Liquitabs 5 mg, 25 mg, 50 mg, 100 mg, 200 mg:
Do not store above 30°C. Keep dry.
Protect liquitabs from light.
Liquitabs 2 mg:
Do not store above 30°C.

Not all presentations are available in every country.

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* Member of the GSK group of companies

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THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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