For the use only of a Registered Medical Practitioner

Lamotaxyl Tablets

(Lamotrigine Tablets 50/100 mg)

COMPOSITION

LAMOTRIGINE TABLETS

Each tablet contains:
Lamotrigine …….50 mg

Each tablet contains:
Lamotrigine …….100 mg

Excipients: Microcrystalline cellulose, lactose monohydrate, sodium starch glycollate, povidone, ferric oxide yellow, purified water, magnesium stearate, talc, colloidal anhydrous silica.

PRODUCT DESCRIPTION

Lamotaxyl Tablets 50 mg

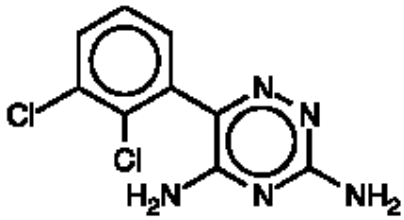
Yellow coloured, capsule shaped, biconvex tablets debossed with 'L' and '50' on either side of the scoreline on one side and a deep breakline on the other side.

Lamotaxyl Tablets 100 mg

Yellow coloured, capsule shaped, biconvex tablets debossed with 'L' and '100' on either side of the scoreline on one side and a deep breakline on the other side.

DESCRIPTION

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. It is chemically designated as 3, 5-diamino-6-(2, 3-dichlorophenyl)-*as*-triazine. Its molecular formula is $C_9H_7N_5Cl_2$, and molecular weight is 256.09.



PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

- Pharmacodynamics

Reported pharmacological studies suggest that lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained repetitive firing of neurones and inhibits release of glutamate (the neurotransmitter which plays a key role in the generation of epileptic seizures). These effects are likely to contribute to the anticonvulsant properties of lamotrigine.

In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

It has been reported that, the central nervous system effects of lamotrigine 240 mg did not differ from placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, increased body sway and produced subjective sedative effects.

It has been reported that single oral doses of 600 mg carbamazepine significantly impaired fine visual motor coordination 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 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics is 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 apparent plasma clearance in healthy subjects is approximately 30 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 apparent plasma half life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

The half life of lamotrigine is greatly affected by concomitant medicinal products. Mean half life is reduced to approximately 14 hours when given with glucuronidation inducing medicinal products such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when coadministered with valproate alone.

Pharmacokinetics in Special Populations

Children: Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean

value of approximately 7 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone.

Infants aged 2 to 26 months: In paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half life was estimated at 23 hours in infants younger than 26 months on enzyme inducing therapy, 136 hours when coadministered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The interindividual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher C_{max} levels are likely to be observed in some children with a body weight below 10 kg.

Elderly: The clearance of lamotrigine did not change to a clinically relevant extent in both young and elderly patients with epilepsy. 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. 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 nine studies with non elderly adults after single doses of 30 to 450 mg.

Renal Impairment: Mean clearances of lamotrigine were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4 hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment.

Hepatic Impairment: In patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment, the median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 mL/min/kg respectively as compared to 0.34 mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment.

Gender: The clearance of lamotrigine is not affected by gender. But, in a case of patients with epilepsy on a stable dose of valproate, mean trough lamotrigine concentrations, increases by 24% to 45% (0.3 to 1.7 µg/mL) in females than in males.

Race: The apparent oral clearance of lamotrigine is 25% lower in non-Caucasians than Caucasians.

INDICATIONS

Lamotaxyl is indicated in:

Epilepsy

Adults: 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-Gaestaut syndrome.

Children (2-12 years): Adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalized seizures including tonic-clonic seizures and the seizures associated with Lennox-Gaestaut syndrome (above 3 years of age only).

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

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

Bipolar Disorder
Adults (≥18 years): Prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes

DOSAGE AND METHOD of ADMINISTRATION

Epilepsy
When concomitant antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or other AEDs are added-on to treatment regimens containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics.

Dosage in monotherapy

Adults >16 years: The initial lamotrigine dose in monotherapy is 25 mg once a day for 2 weeks, followed by 50 mg once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or as 2 divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.
Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded.

Add-on Therapy

Adults >12 years: see Table 1

Table 1: Recommended treatment regimen in Epilepsy for Adults			
Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Maintenance Dose

Monotherapy (>16 years of age)		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 years of age)		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 Phenobarbital primidone or with other inducers of lamotrigine glucuronidation.	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 lamotrigine is currently not known, the treatment regimen as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.				

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

In those patients taking concomitant AEDs or other medication that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial lamotrigine dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in 2 divided doses for 2 weeks.

Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400 mg/day given in 2 divided doses.

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

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

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded.

Children aged 2 to 12 year: see Table 2

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

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Maintenance Dose
Add-on therapy with valproate regardless of any other concomitant medication	0.15 mg/kg* (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every 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 phenobarbital primidone or with other inducers of lamotrigine glucuronidation.	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 in 2 divided doses) to a maximum of 400 mg/day.
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 - 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, 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 1-2 mg, then 2 mg lamotrigine may be taken on alternate days for the first 2 weeks. If the calculated daily dose in patient taking valproate is <1 mg, then lamotrigine should not be administered. *Where 5 mg tablets are the lowest marketed strength: If the calculated daily dose in patients taking valproate is 2.5-5 mg, then 5 mg may be taken on alternate days for the first 2 weeks. If the calculated daily dose in patients taking valproate is <2.5 mg, then lamotrigine should not be administered. It is not possible to accurately initiate lamotrigine therapy using the recommended dosing guidelines in paediatric patients weighing <17 kg.				

In patients taking valproate with/without any other AED, the initial lamotrigine dose is 0.15 mg/kg body weight/day given once a day for 2 weeks, followed by 0.3 mg/kg/day once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in 2 divided doses, with a maximum of 200 mg/day.

In those patients taking concomitant AEDs or other medications that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial lamotrigine dose is 0.6 mg/kg body weight/day given in 2 divided doses for 2 weeks, followed by 1.2 mg/kg/day given in 2 divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1-2 weeks until the optimal response is

achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in 2 divided doses, with a maximum of 400 mg/day.

In patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in 2 divided doses for 2 weeks, followed by 0.6 mg/kg/day given once a day or in 2 divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10 mg/kg/day given once a day or in 2 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.

It is likely that patients 2-6 years will require a maintenance dose at the higher end of the recommended range.

Children <2 years: There is insufficient information on the use of lamotrigine in children <2 years.

Bipolar Disorder:

Adults greater than or equal to 18 years: Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded.

Lamotrigine is recommended for use in bipolar patients at risk for future depressive episode.

The following transition regimen should be followed to prevent recurrence depressive episodes. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilization dose over 6 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 lamotrigine in mania has not been conclusively established.

Table 3: Recommended Dose Escalation to the Maintenance Total Daily Stabilisation Dose for Adults (<18 years) Treated for Bipolar Disorder.

Treatment Regimen	Weeks 1-2	Weeks 3-4	Week 5	Target Stabilisation Dose (Week 6)**
Adjunct therapy with inhibitors of lamotrigine glucuronidation eg, valproate	12.5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or in 2 divided doses)	100 mg (once a day or in 2 divided doses) (maximum daily dose of 200 mg)
Adjunct therapy with inducers of	50 mg (once a day)	100 mg (2 divided doses)	200 mg (2 divided doses)	300 mg in week 6, increasing to 400

Lamotrigine glucuronidation in patients not taking inhibitors eg, valproate This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of lamotrigine glucuronidation				mg/day if necessary in week 7) (2 divided doses)
Monotherapy with lamotrigine 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 in 2 divided doses)	100 mg (once a day or in 2 divided doses)	200 mg (Range 100-400 mg) (once a day or in 2 divided doses)
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used. **The target stabilisation dose will alter depending on clinical response.				

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule as follows (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*
Following withdrawal of inhibitors of lamotrigine	Double the stabilisation dose, not exceeding 100	Maintain this dose (200 mg/day) (2 divided doses)	

glucuronidation eg, valproate	mg/week ie, 100 mg/day target stabilisation dose will be increased in week 1- 200 mg/day		
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	400 mg 300 mg 200 mg	300 mg 225 mg 150 mg	200 mg 150 mg 100 mg
Following withdrawal of other psychotropic or AED drugs in patients not taking significant inducers or inhibitors of lamotrigine glucuronidation (including lithium, bupropion, olanzapine, oxcarbazepine)	Maintain target dose achieved in dose escalation (200 mg/day) (2 divided doses) (Range 100-400 mg)		
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen asrecommended for lamotrigine with concurrent valproate, should be used. *Dose may be increased to 400 mg/day as needed.			

Adjustment in Lamotrigine Daily Dosing in Patients with Bipolar Disorder Following Addition of Other Medications: There is no clinical experience adjusting the lamotrigine daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (see Table 5 as follows).

Table 5: Adjustment of Lamotrigine Daily Dosing in Patients with Bipolar Disorder Following the Addition of Other Medications.

Treatment Regimen	Current Lamotrigine Stabilisation Dose (mg/day)	Week 1	Week 2	Week 3 Onwards
Addition of	200 mg	100 mg	Maintain this dose (100 mg/day)	

inhibitors of lamotrigine glucuronidation eg, valproate, depending on original dose of lamotrigine	300 mg 400 mg	150 mg 200 mg	Maintain this dose (150 mg/day) Maintain this dose (200 mg/day)	
Addition of inducers of lamotrigine glucuronidation in patients not taking valproate and depending on original dose of lamotrigine. This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of lamotrigine glucuronidation	200 mg 150 mg 100 mg	200 mg 150 mg 100 mg	300 mg 225 mg 150 mg	400 mg 300 mg 200 mg
Addition of other psychotropic or AED drugs with no significant pharmacokinetic interaction with lamotrigine eg, lithium, bupropion, olanzapine, oxcarbazepine	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known				

Discontinuation of Lamotrigine 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 lamotrigine versus placebo. Therefore, patients may terminate lamotrigine without a stepwise reduction of dose.

Children and Adolescents (<18 years): Lamotrigine is not indicated for use in bipolar disorder in children and adolescents <18 years. Safety and efficacy of lamotrigine in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

Special Patient Population:

Women Taking Hormonal Contraceptives:

Starting Lamotrigine in Patients Already Taking Hormonal Contraceptives: Although an oral contraceptive has been shown to increase the clearance of lamotrigine, no adjustments to the recommended dose escalation guidelines for lamotrigine 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 eg, valproate; whether lamotrigine is added to an inducer of lamotrigine glucuronidation eg, carbamazepine, phenytoin, phenobarbital, primidone or rifampin; or whether lamotrigine is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (see Table 1 for epilepsy and Table 3 for bipolar patients).

Starting Hormonal Contraceptives in Patients Already Taking Maintenance Doses of Lamotrigine and not Taking Inducers of Lamotrigine Glucuronidation: The maintenance dose of lamotrigine may need to be increased by as much as 2-fold according to the individual clinical response.

Stopping Hormonal Contraceptives in Patients Already Taking Maintenance Doses of Lamotrigine and not Inducers of Lamotrigine Glucuronidation: The maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual response.

Elderly (>65 years):

No dosage adjustment from recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population.

Hepatic Impairment:

Initial, 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.

Renal Impairment:

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

Administration

LAMOTAXYL TABLETS should be swallowed whole with a little water.

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

Restarting Therapy

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

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

CONTRAINDICATION

Lamotaxyl is contraindicated in patients who have demonstrated hypersensitivity to the lamotrigine or any of the excipients of this medicinal product.

WARNINGS AND PRECAUTIONS

Haemophagocytic lymphohistiocytosis (HLH)

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

Brugada type ECG

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

Skin Rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self limiting; however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These

have included potentially life threatening rashes such as Stevens–Johnson syndrome and toxic epidermal necrolysis.

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 reaction to lamotrigine treatment 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 lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy

- concomitant use of valproate.

Caution is also required when treating patients with a history of allergy or rash to other AEDs as the frequency of non serious rash after treatment with lamotrigine 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 lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

Rash also has been reported as a part of hypersensitivity syndrome associated with a variable patters of systemic symptoms including fever, lymphadenopathy, facial edema 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 multi organ failure, It is important to note that early manifestations of hypersensitivity leg., fever, lymphadenopathy may be present even though rash is non evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative etiology cannot be established.

Multiorgan Hypersensitivity Reactions and Organ Failure

Multiorgan hypersensitivity reactions, also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported with lamotrigine. Some have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, haematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

Fatalities associated with acute multiorgan failure and various degrees of hepatic failure have been reported in adult and pediatric patients who received lamotrigine in epilepsy. Rare fatalities from multiorgan failure have also been reported in postmarketing use. Isolated liver failure without rash or involvement of other organs has also been reported with lamotrigine. It is important to note that early manifestations of

hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Lamotrigine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

Blood Dyscrasias

There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

Suicidal Behaviour and Ideation

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of clinical studies of AEDs 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 and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including lamotrigine. Therefore 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.

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.

Use in Patients with Bipolar Disorder

Acute Treatment of Mood Episodes: Safety and effectiveness of lamotrigine in the acute treatment of mood episodes have not been established.

Children and Adolescents (less than 18 years of age): Safety and effectiveness of lamotrigine in patients below the age of 18 years with mood disorders have not been established.

Clinical Worsening and Suicide Risk Associated with Bipolar Disorder: Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for 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.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

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/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Prescriptions for lamotrigine should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Overdoses have been reported for lamotrigine, some of which have been fatal.

Aseptic Meningitis

Therapy with lamotrigine increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate. Postmarketing cases of aseptic meningitis have been reported in pediatric and adult patients taking lamotrigine for various indications. Symptoms upon presentation have included headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills, altered consciousness, and somnolence were also noted in some cases. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment. In most cases, symptoms were reported to resolve after discontinuation of lamotrigine. Re-exposure resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-initiation of treatment) that were frequently more severe. Some of the patients treated with lamotrigine who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.

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

Concomitant Use with Oral Contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately twofold resulting in decreased lamotrigine levels. A decrease in lamotrigine

levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as twofold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment. Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first line therapy (for example, continuous hormonal contraceptives or non hormonal methods).

Clinicians should exercise appropriate clinical management of woman starting or stopping hormonal contraceptives during lamotrigine therapy and lamotrigine dosing adjustments may be needed.

Effects of lamotrigine on hormonal contraceptive efficacy

An interaction study reported in 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. 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 lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Withdrawal Seizures

As with other AEDs, lamotrigine should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In reported clinical studies in patients with Bipolar Disorder, few patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid withdrawal, the dose of lamotrigine should be tapered over a period of at least 2 weeks (approximately 50% reduction per week).

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 lamotrigine. A clinically significant worsening of seizure frequency instead of an improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Myoclonic seizures may be worsened by lamotrigine. There is a suggestion in the data that responses in combination with enzyme inducers are less than in combination with non-enzyme inducing antiepileptic agents. The reason is unclear. In children taking lamotrigine for the treatment of typical absence seizures, efficacy may not be maintained in all patients.

Status Epilepticus
In reported clinical studies, only few adult patients treated with lamotrigine had episodes that could unequivocally be described as status epilepticus. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Sudden Unexplained Death in Epilepsy (SUDEP)
During the clinical development of lamotrigine, sudden and unexplained deaths have been reported among a cohort of epilepsy patients. Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. There is a similarity of estimated SUDEP rates in patients receiving lamotrigine and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

Addition of Lamotrigine to a Multidrug Regimen That Includes Valproate

Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence.

Binding in the Eye and Other Melanin-Containing Tissues

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

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

Dihydrofolate reductase
Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long term therapy. However, during prolonged human dosing, lamotrigine 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 reported 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
Lamotrigine should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

Excipient of Lamotaxyl Tablets
Lamotaxyl tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Development in children
There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioral developments in children.

Laboratory Tests
The value of monitoring plasma concentrations of lamotrigine in patients treated with lamotrigine has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs, monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

Effects on ability to drive and use machines
As there is individual variation in response to all AED therapy, patients taking lamotrigine to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.

No studies on the effects on the ability to drive and use machines have been performed. Reported clinical studies have demonstrated that the effect of lamotrigine on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In reported clinical studies with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

DRUG 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 medicinal products on glucuronidation of lamotrigine

Medicinal products that significantly inhibit glucuronidation of lamotrigine	Medicinal products that significantly induce glucuronidation of lamotrigine	Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine
Valproate	Phenytoin	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbital	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate

	Ethinylestradiol/ levonorgestrel combination*	Zonisamide
	Atazanavir/ritonavir	Lithium
		Buproprion
		Olanzapine
		Aripiprazole

* Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Interactions involving AEDs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used.

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. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used.

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

There are reports in the literature of decreased lamotrigine levels when lamotrigine was given in combination with oxcarbazepine. However, in a study reported 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. Therefore in patients receiving concomitant therapy with oxcarbazepine, the treatment regimen for lamotrigine adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation should be used.

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 clinical studies. 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.

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 in patients with epilepsy.

Although changes in the plasma concentrations of other antiepileptic drugs have been reported, 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

The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to healthy subjects were not altered by coadministration of 100 mg/day lamotrigine.

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

Olanzapine at 15 mg dose 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. Following the coadministration 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 vitro experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally inhibited by coincubation with amitriptyline, bupropion, clonazepam, haloperidol or lorazepam. These experiments also suggested that metabolism of lamotrigine was unlikely to be inhibited by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. In addition, a study of bufuralol metabolism using human liver microsome preparations suggested that lamotrigine would not reduce the clearance of medicinal products metabolised predominantly by CYP2D6.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics:

Oral contraceptive pill (30 mcg ethinylestradiol/150 mcg levonorgestrel) 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:

Co-administration of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown. Vaginal bleeding was reported by some volunteers. The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products

Use with Rifampicin
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 appropriate treatment regimen should be used.

Use with lopinavir/ritonavir
No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing lopinavir/ritonavir therapy.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed.

Use with atazanavir/ritonavir
No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing atazanavir/ritonavir therapy.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed.

Others
Data from *in vitro* assessment demonstrated 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 in vitro inhibitor of OCT 2 than cimetidine, with IC_{50} values of 53.8 μM and 186 μM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

The clinical significance of this has not been clearly defined; however care should be taken in patients co-administered with these medicinal products.

SIDE EFFECTS/UNDESIRABLE EFFECTS

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the reported data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine.

Epilepsy

Blood and lymphatic system disorders

Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, and agranulocytosis, haemophagocytic lymphohistiocytosis (see WARNINGS AND PRECAUTIONS).

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

Not known: lymphadenopathy

Immune system disorders

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

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example 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 lamotrigine discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common: irritability, aggression

Very rare: confusion, hallucinations, tics.

Not known: nightmares

Nervous system disorders

During monotherapy clinical trials:

Very common: headache.

Common: somnolence, dizziness, tremor, insomnia.

Uncommon: ataxia.

Rare: Nystagmus

During other clinical experience:

Very common: somnolence, ataxia, headache, dizziness

Common: nystagmus, tremor, insomnia

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

Not known: Aseptic meningitis.

Eye disorders

Uncommon: diplopia, blurred vision.

Rare: conjunctivitis.

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea

Hepato‑biliary disorders

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

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

Skin and subcutaneous tissue disorders

Very common: skin rash.

Uncommon: alopecia

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms

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 lamotrigine.

Nervous system disorders

Very common: headache.

Common: agitation, somnolence, dizziness.

Gastrointestinal disorders

Common: dry mouth

Skin and subcutaneous tissue disorders

Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Musculoskeletal and connective tissue disorders

Common: arthralgia.

General disorders and administration site conditions

Common: pain, back pain.

Other adverse events reported with the use of lamotrigine are following:

Respiratory System: Infrequent: Yawn. Rare: Hiccup and hyperventilation. Not known: Apnoea.

Immunologic: Not known: Vasculitis.

Non-site Specific: Progressive immunosuppression

Special Senses: Frequent: Amblyopia. Infrequent: Abnormality of accommodation, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect.

Urogenital System: Infrequent: Abnormal ejaculation, haematuria, impotence, menorrhagia, polyuria, and urinary incontinence. Rare: Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, and urinary urgency.

Post-marketing
Blood and lymphatic system disorders
Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

USE IN SPECIAL POPULATIONS

- Pregnancy

Risk related to antiepileptic drugs in general

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with AEDs compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple AEDs is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

<u>Risk related to lamotrigine</u>

Pregnancy
Post marketing data from several prospective pregnancy registries have documented outcomes in over 2000 women exposed to lamotrigine 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 are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity.

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

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

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

Lactation
Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother's. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. Among a limited group of exposed infants, no adverse effects were observed.

The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects.

Fertility
Animal experiments did not reveal impairment of fertility by lamotrigine.

- Pediatric Use

Lamotrigine is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures.

Safety and efficacy of lamotrigine, used as adjunctive treatment for partial seizures, were not demonstrated in a reported clinical study in very young pediatric patients (1 to 24 months). Lamotrigine was associated with an increased risk for infectious adverse reactions and respiratory adverse reactions. Infectious adverse events included: bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse events included nasal congestion, cough, and apnea.

Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not been established.

- Geriatric Use

Reported studies available in the public domain of lamotrigine for epilepsy and in Bipolar Disorder did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects or exhibit a different safety profile than that of younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the

dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

- Renal impairment

Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4 hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment.

- Hepatic impairment

Hepatic Impairment: In patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment, the median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 mL/min/kg respectively as compared to 0.34 mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment.

OVERDOSAGE

Symptoms and signs:
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.

Treatment:
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session.

STORAGE
Store below 30°C, protected from moisture

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

PACKING
Blister pack of 28's tablets and 10 x 10's

Manufactured by:
Sun Pharmaceutical Ind. Ltd.
Industrial Area-3,
Dewas-455 001

Product Registration Holder:
RANBAXY (MALAYSIA) SDN. BHD.
(a Sun Pharma company)
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah,
Malaysia.

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