LAMICTAL

Version GDSv50-IPIv 27

LAMICTAL

Lamotrigine

Qualitative and Quantitative Composition

Tablets

LAMICTAL, 25, 50, 100 and 200 mg.

Dispersible/chewable tablets

LAMICTAL, 2, 5, 25, 50, 100 and 200 mg.

Clinical Information

Directions

Epilepsy

Adults and Adolescents (Over 12 Years of Age)

LAMICTAL is indicated for use as adjunct therapy or monotherapy in the treatment of epilepsy, for partial and generalized seizures, including tonic-clonic seizures and seizures associated with Lennox-Gastaut Syndrome.

Children (2 to 12 Years of Age)

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

Once epileptic control has been achieved during adjunctive therapy, concomitant antiepileptic drugs (AEDs) may be withdrawn and patients may continue ***LAMICTAL*** monotherapy.

LAMICTAL is indicated as monotherapy in the treatment of typical absence seizures.

If LAMICTAL 2 mg dispersible/chewable tablets is not available and the calculated dose in children is less than 2.5 mg per day, ***LAMICTAL*** cannot be used. DO NOT attempt to administer partial amounts of chewable/dispersible tablets

Bipolar disorder

Adults (18 years of age and older)

LAMICTAL is indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

Dosage and Administration

Pharmaceutical form

Dispersible/chewable tablets and tablets.

LAMICTAL tablets should be ingested whole, and should not be chewed or bitten.

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

Do not attempt to administer partial amounts of the chewable/dispersible tablets.

If it is not possible to divide the calculated ***dose of LAMICTAL***, for example for use in children (epilepsy only) or patients with liver damage, into multiple tablets of lower strength, the dose to be administered should be equal to the nearest lower concentration of whole tablets.

Restart of Therapy

Prescribers should evaluate the need for titration up to maintenance dose when restarting LAMICTAL in patients who have discontinued ***LAMICTAL*** for any reason, as the risk of serious rash is associated with high initial doses and exceeding the recommended dose titration of ***LAMICTAL*** *(see WARNINGS and PRECAUTIONS)*. The longer the interval from the previous dose, the greater consideration should be given to titration up to the maintenance dose. When the interval since discontinuation of LAMICTAL exceeds five half-lives *(see Pharmacokinetics),* ***LAMICTAL*** should generally be titrated to the maintenance dose according to the appropriate schedule.

It is recommended not to restart ***LAMICTAL*** in patients who have discontinued it due to rash associated with prior ***LAMICTAL*** treatment unless the potential benefit clearly outweighs the risks.

Epilepsy

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

Dosage in Monotherapy for Epilepsy

Adults and Adolescents (Over 12 Years of Age) (see Table 1)

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

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

The starting dose of ***LAMICTAL*** as monotherapy to treat typical absence seizures consists of 0.3 mg/kg bw/day administered once daily or in two divided doses over two weeks, followed by 0.6 mg/kg/day administered once daily or in two divided doses for two weeks. Therefore, the dose should be increased to a maximum of 0.6 mg/kg every one to two weeks until an optimal response is achieved. The usual maintenance dose for optimal response consists of 1 to 10 mg/kg/day administered once daily or in two divided doses, although some patients with typical absence seizures have required higher doses to achieve the desired response.

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

Dosage in Aggregate Therapy for Epilepsy

Adults and Adolescents (Over 12 Years of Age) (see Table 1)

In patients taking valproate with/without another AED, the starting dose of ***LAMICTAL*** is 25 mg every other day for two weeks, followed by 25 mg once daily for two weeks. Thereafter, the dose should be increased by a maximum of 25 to 50 mg within one to two weeks until optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day administered once daily or in two divided doses.

In those patients taking concomitant AEDs or other medicinal products (*see Interactions*) that induce glucuronidation of lamotrigine with/without other AEDs (except valproate), the starting dose of ***LAMICTAL*** is 50 mg once daily for two weeks, followed by 100 mg/day administered in two divided doses over two weeks.

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

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

In those patients taking other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions), the starting dose of ***LAMICTAL*** is 25 mg once daily for two weeks, followed by 50 mg once daily for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg within one to two weeks until optimal response is achieved. The usual maintenance dose to achieve an optimal response is 200 mg/day administered once daily or as two divided doses.50 a100 a

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

Treatment regimen		Weeks 1 - 2	Weeks 3 - 4	Maintenance Dosage
Monotherapy		25 mg (once daily)	50 mg (once daily)	100 – 200 mg (once daily or two divided doses) To achieve maintenance, doses can be increased by 50 – 100 mg in one to two weeks.
Added valproate therapy regardless of any concomitant medications		12.5 mg (25 mg given every other day)	25 mg (once daily)	100 – 200 mg (once daily or two divided doses) To achieve maintenance, doses can be increased by 25 – 50 mg in one to two weeks.
Aggregate therapy without valproate	This dosing regimen should be used with: Phenytoin Carbamazepine Phenobarbital Primidone Or with other inducers of lamotrigine glucuronidation (*see Interactions*).	50 mg (once daily)	100 mg (two divided doses)	200 – 400 mg (two divided doses) To achieve maintenance, doses can be increased by 100 mg in one to two weeks
	This dosing regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*).	25 mg (once daily)	50 mg (once daily)	100 – 200 mg (once daily or two divided doses) To achieve maintenance, doses can be increased by 50 – 100 mg in one to two weeks.
In patients taking AEDs for whom the pharmacokinetic interaction with LAMICTAL is currently unknown (see Interactions), the recommended LAMICTAL treatment regimen with concurrent valproate should be used.				

Because of the risk of rash, the initial dose and subsequent dose titration should not be exceeded (*see WARNINGS and PRECAUTIONS*).

Children (2 to 12 years of age) (see table 2)

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

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

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

To ensure that the therapeutic dose is maintained, the child's weight should be monitored and the dose reviewed as changes in weight occur.

Table 2: Recommended treatment regimen in EPILEPSY for children aged 2-12 years (total daily dose in mg/kg bw/day). **

Treatment regimen		Weeks 1 - 2	Weeks 3 - 4	Maintenance Dosage
Monotherapy in typical absence seizures		0.3 mg/kg (once daily or two divided doses)	0.6 mg/kg (once daily or two divided doses)	Increments of 0.6 mg/kg every one to two weeks to reach a maintenance dose of 1 - 10 mg/kg (once daily or two divided doses) for a maximum of 200 mg/day.
Added valproate therapy regardless of any concomitant medications		0.15 mg/kg* (once daily)	0.3 mg/kg (once daily)	Increments of 0.3 mg/kg over one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once daily or two divided doses) up to a maximum of 200 mg/day.
Aggregate therapy without valproate	This dosing regimen should be used with: Phenytoin Carbamazepine Phenobarbital Primidone Or with other inducers of lamotrigine glucuronidation (see Interactions).	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	Increments of 1.2 mg/kg over one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (once daily or two divided doses) up to a maximum of 400 mg/day.
	This dosing regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions).	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	Increments of 0.6 mg/kg over one to two weeks to achieve a maintenance dose of 1 – 10 mg/kg (once daily or two divided doses) up to a maximum of 200 mg/day.
In patients taking AEDs for whom the pharmacokinetic interaction with lamotrigine is currently unknown (see Interactions), the recommended treatment regimen for lamotrigine with concurrent valproate should be used. *(Where 2 mg tablets are the lowest concentration available) If the calculated daily dose in patients taking valproate is between 2.5 and 5 mg, then 5 mg can be taken every other day for the first two weeks. *(Where 5 mg tablets are the lowest concentration available)If the calculated daily dose in patients taking valproate is less than 2.5 mg, LAMICTAL should not be used. DO NOT attempt to administer partial amounts of the dispersible/chewable tablets. **If the calculated dose of LAMICTAL cannot be reached using whole tablets, the dose should be rounded to the nearest whole tablet.				

Because of the risk of rash, the initial dose or subsequent dose escalation should not be exceeded (*see WARNINGS AND PRECAUTIONS*).

Patients aged two to six years may require a maintenance dose at the higher end of the recommended range.

Monotherapy and Additive Therapy for Epilepsy

Children Under 2 Years of Age

The use of lamotrigine as monotherapy in children younger than 2 years of age or as add-on therapy in children younger than 1 month of age is not yet being studied. The safety and efficacy profiles of lamotrigine given as add-on therapy in the treatment of partial seizures in children 1 month through 2 years of age have not yet been established *(*see Clinical Studies). Therefore, the use of ***LAMICTAL*** in children under 2 years of age is not recommended.

Bipolar disorder

Adults (18 Years of Age and Older)

Because of the risk of rash, the initial dose and subsequent dose titration should not be exceeded (*see WARNINGS and PRECAUTIONS*).

LAMICTAL is recommended for use in bipolar patients at risk of a future depressive episode.

The following transitional regimen should be followed to prevent recurrence of depressive episodes. The transitional regimen involves titration of the ***LAMICTAL*** dose to a maintenance stabilization dose within six weeks (see Table 3) after which other psychotropic and/or antiepileptic drugs may be withdrawn, if clinically indicated (see Table 4).

Adjunctive therapy for the prevention of manic episodes should be considered, as the efficacy of ***LAMICTAL*** in mania has not been conclusively established.

Table 3: Recommended dose titration of the total daily dose of maintenance stabilization for adults (18 years of age and older) treated for BIPOLAR DISORDER

Treatment regimen	Weeks 1-2	Weeks 3-4	Week 5	Desired stabilization dose (Week 6)**
a) Adjunctive therapy with lamotrigine glucuronidation inhibitors e.g., valproate	12.5 mg (25 mg given every other day)	25 mg (once daily)	50 mg (once daily or two divided doses)	100 mg (once daily or two divided doses) (maximum daily dose of 200 mg)
b) Adjunctive therapy with inducers of lamotrigine glucuronidation in patients who do NOT take inhibitors such as valproate This dosing regimen should be used with: Phenytoin Carbamazepine Phenobarbital Primidone Or with other inducers of lamotrigine glucuronidation (see Interactions)	50 mg (once daily)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg at week 6, increasing to 400 mg/day at week 7 if needed (two divided doses)
c) ***LAMICTAL*** monotherapy or adjunctive therapy in patients taking other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	25 mg (once daily)	50 mg (once daily or two divided doses)	100 mg (once daily or two divided doses)	200 mg (Range 100400mg) (once daily or two divided doses)
NOTE: In patients taking AEDs for whom the pharmacokinetic interaction with lamotrigine is currently unknown, ***LAMICTAL*** recommended dose titration with concurrent valproate should be used. **The desired stabilization dose will change depending on clinical response.				

a. Adjunctive therapy with lamotrigine glucuronidation inhibitors e.g., valproate

In patients taking concomitant glucuronidation inhibitor drugs such as valproate, the starting dose of ***LAMICTAL*** is 25 mg every other day for two weeks, followed by 25 mg once daily for two weeks. The dose should be increased to 50 mg once daily (or in two divided doses) at week 5. The usual dose desired to achieve optimal response is 100 mg/day administered once daily or in two divided doses. However, the dose may be increased to a maximum daily dose of 200 mg, depending on clinical response.

b. Adjunctive therapy with inducers of lamotrigine glucuronidation in patients who are NOT taking inhibitors such as valproate. This dosing regimen should be used with phenytoin, carbamazepine, phenobarbital, primidone, and other drugs recognized to induce lamotrigine glucuronidation (*see Interactions*).

In patients currently taking drugs that induce lamotrigine glucuronidation and NOT taking valproate, the starting dose of ***LAMICTAL*** is 50 mg once daily for two weeks, followed by 100 mg/day given as two divided doses for two weeks. The dose should be increased to 200 mg/day administered as two divided doses at week 5. At week 6, the dose may be increased to 300 mg/day however the usual dose desired to achieve optimal response is 400 mg/day administered in two divided doses which can be administered from week 7.

c. ***LAMICTAL*** monotherapy OR adjunctive therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions).

The starting dose of ***LAMICTAL*** is 25 mg once daily for two weeks , followed by 50 mg once daily (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day at week 5. The usual dose desired to achieve optimal response is 200 mg/day administered once daily or as two divided doses. However, a range of 400 mg was used in clinical trials.100 a

Once the desired daily dose for maintenance stabilization has been achieved, other psychotropic medications may be withdrawn as indicated in the dosing schedule shown below (see Table 4).

Table 4: Total daily dose for maintenance stabilization in adults (18 years of age and older) with bipolar disorder following withdrawal of concomitant psychotropic or antiepileptic drugs

Treatment regimen	Week 1	Week 2	Week 3 onwards*
(a) Following withdrawal of lamotrigine glucuronidation inhibitors e.g., valproate	Twice the stabilization dose, not to exceed 100 mg/week For example the desired stabilization dose of 100 mg/day will be increased at week 1 to 200 mg/day.	Maintain this dose (200 mg/day) (two divided doses)	
(b) After withdrawal of inducers of lamotrigine glucuronidation depending on the original dose. This dosing regimen should be used with: Phenytoin Carbamazepine Phenobarbital 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 medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	Maintain the desired dose achieved with dose escalation (200 mg/day) (two divided doses) (Range 100-400 mg)		
NOTE: In patients taking AEDs for whom the pharmacokinetic interaction with lamotrigine is currently unknown, the recommended treatment regimen for LAMICTAL is initially to maintain the current dose and adjust ***LAMICTAL*** treatment based on clinical response. * As needed, the dose may be increased up to 400 mg/day			

a. Following withdrawal of adjunctive therapy with lamotrigine glucuronidation inhibitors e.g., valproate

Once valproate is finished, the dose of ***LAMICTAL*** should be increased to twice the original desired stabilization dose and maintained at that rate.

b. After withdrawal of adjunct therapy with inducers of lamotrigine glucuronidation, depending on the original maintenance dose. This regimen should be used with phenytoin, carbamazepine, phenobarbital, primidone, or other drugs known to induce glucuronidation of ***LAMICTAL*** (see Interactions).

As glucuronidation inducers are withdrawn , the dose of ***LAMICTAL*** should be gradually reduced over three weeks.

c. Following withdrawal of adjunctive therapy with other drugs that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions).

Throughout the withdrawal of other medications, the desired dose achieved with the dose escalation program should be maintained.

Adjustment of the daily dose of *LAMICTAL* in patients with BIPOLAR DISORDER after adding other medicinal products

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

Table 5: Adjustment of daily dosage of *LAMICTAL* in adults (18 years of age and older) with BIPOLAR DISORDER after adding other medications

Treatment regimen	Current dose of *LAMICTAL* for stabilization (mg/day)	Week 1	Week 2	Week 3 onwards
(a) Addition of lamotrigine glucuronidation inhibitors e.g., valproate, depending on the 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 the original dose of ***LAMICTAL***. This dosing regimen should be used with: Phenytoin Carbamazepine Phenobarbital 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 medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	Maintain the desired dose achieved with dose titration (200 mg/day) (range 100-400 mg)			
NOTE: In patients taking AEDs for whom pharmacokinetic interactions with lamotrigine are currently unknown, the recommended ***LAMICTAL*** treatment regimen with concurrent valproate should be used.				

***Discontinuation of LAMICTAL* in Adult Patients with Bipolar Disorder**

In clinical trials, there was no increase in the incidence, severity or type of adverse experiences following abrupt discontinuation of ***LAMICTAL*** compared to placebo. Therefore, patients can terminate ***LAMICTAL*** without dose tapering

Children and Adolescents (Under 18 Years of Age)

LAMICTAL is not indicated for bipolar disorder in children and adolescents younger than 18 years of age (*see WARNINGS and PRECAUTIONS*). The safety and efficacy of ***LAMICTAL*** for bipolar disorder in this age group have not been established. Therefore, no dosing recommendations can be made.

General Dosing Recommendations for *LAMICTAL* in Special Patient Populations

Women Taking Hormonal Contraceptives

a. Initiation of ***LAMICTAL*** in patients already taking hormonal contraceptives:

Although oral contraceptive has been shown to increase the elimination of lamotrigine (*see Warnings and Precautions and Interactions*), adjustments to the recommended dose titration guidelines for ***LAMICTAL*** based on hormonal contraceptive use alone will not be necessary. Dose escalation should follow recommended guidelines based on whether lamotrigine is added to valproate (a lamotrigine glucuronidation inhibitor), or to a lamotrigine glucuronidation inducer, or whether ***LAMICTAL*** is added in the absence of valproate, or any inducer of lamotrigine glucuronidation (see Table 1 for patients with epilepsy and Table 3 for patients with bipolar disorder).

b. Initiation of hormonal contraceptives in patients already taking the maintenance dose of ***LAMICTAL*** and NOT taking inducers of lamotrigine glucuronidation:

In most cases it will be necessary to increase the maintenance dose of ***LAMICTAL*** up to twice (*see Warnings and Precautions and Interactions*). It is recommended that, from the moment hormonal contraceptive use is initiated, the dose of lamotrigine be increased by 50 to 100 mg/day each week, according to the clinical response of each individual. Dose increases should not exceed this rate unless clinical response supports larger increases.

c. Discontinuation of hormonal contraceptives in patients already taking the maintenance dose of ***LAMICTAL*** and NOT taking inducers of lamotrigine glucuronidation:

In most cases it will be necessary to decrease the maintenance dose of ***LAMICTAL*** by up to 50% (*see Warnings and Precautions and Interactions*). It is recommended to gradually decrease the daily dose of lamotrigine by 50 to 100 mg each week (at a rate not to exceed 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise.

Use with Atazanavir/Ritonavir

Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (see Interactions), no adjustments to the recommended ***LAMICTAL*** dose titration guidelines should be necessary based solely on the use of atazanvir/ritonavir. Dose titration should follow recommended guidelines based on whether LAMICTAL is added to valproate (a lamotrigine glucuronidation inhibitor), or to a lamotrigine glucuronidation inducer, or whether ***LAMICTAL*** is added in the absence of valproate or a lamotrigine glucuronidation inducer.

In patients already taking maintenance doses of LAMICTAL who are not taking glucuronidation inducers, the dose of ***LAMICTAL*** may need to be increased if atazanavir/ritonavir is added , or reduced if atazanavir/ritonavir is discontinued.

Elderly (Over 65 Years of Age)

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

Liver damage

Generally, the initial, titration and maintenance doses should be reduced by approximately 50% in patients with moderate liver damage (Child-Pugh grade B) and 75% in severe liver damage (Child-Pugh grade C). Titration and maintenance doses should be adjusted according to clinical response (*see Pharmacokinetics*).

Renal insufficiency

Care should be taken when administering ***LAMICTAL*** to patients with renal failure. For patients with end-stage renal failure, initial doses of ***LAMICTAL*** should be based on the patient's AED regimen; reduction of maintenance doses may be effective for patients with significant impairment of renal function (*see WARNINGS and PRECAUTIONS*). For more detailed information on pharmacokinetics (*see Pharmacokinetics*).

Contraindications

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

Warnings and Precautions

Exanthema

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiating ***treatment with LAMICTAL***. Most are mild, self-limiting rashes, however, serious rashes requiring hospitalization and discontinuation of ***LAMICTAL*** have also been reported. These have included potentially fatal rashes such as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (*see Adverse Reactions*).

In adults enrolled in studies using ***current LAMICTAL*** dosing recommendations , the incidence of serious rashes is approximately 1 in 500 in epileptic patients. About half of these cases were reported as SJS (1 in 1000).

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

The risk of serious rash is higher in children than in adults.

Available data from a number of studies suggest that the incidence of rashes associated with hospitalization in children is 1 in 300 to 1 in 100.

In children, the initial presentation of a rash may be mistaken for an infection, and clinicians should consider the possibility of a drug reaction in children who develop symptoms of rash and fever during the first eight weeks of therapy.

Additionally, the overall risk of rash appears to be closely 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 should be exercised when treating patients with a history of rashes or allergies to other antiepileptic drugs, as the frequency of non-severe rashes after ***LAMICTAL*** treatment was approximately three times higher in these patients than in those without such a history.

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

Rash has also been reported as part of a drug reaction with Eosinophilia and Systemic Symptoms (DRESS); Also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial edema and blood, liver and kidney abnormalities and aseptic meningitis (see ADVERSE REACTIONS). The syndrome shows a broad spectrum in clinical severity, and can, rarely, lead to disseminated intravascular coagulation (DIC) and multiple organ failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though the rash is not evident. If these signs and symptoms are present, the patient should be evaluated immediately and ***LAMICTAL*** discontinued if an alternative etiology cannot be established.

In most cases, aseptic meningitis was reversible upon withdrawal of the drug, but recurrence occurred in certain cases upon reexposure of patients to lamotrigine. The new exposure caused a rapid return of symptoms, which were often more severe. Lamotrigine should not be restarted in patients who have discontinued lamotrigine due to the development of aseptic meningitis associated with prior lamotrigine therapy.

Hemophagocytic Lymphohistiocytosis (HLH)

HLH occurred in patients taking ***LAMICTAL*** (see ADVERSE REACTIONS). HLH is a potentially life-threatening pathological immune activation syndrome characterized by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, elevated serum ferritin concentrations, hypertriglyceridemia, and abnormalities of liver function and coagulation. Symptoms usually develop within 4 weeks after treatment begins.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. ***LAMICTAL*** should be discontinued, unless an alternative etiology can be established.

Risk of Suicide

Symptoms of depression and/or bipolar disorder may occur in patients with epilepsy, and there are indications that patients with epilepsy and bipolar disorder are at high risk of developing suicidality.

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

Cases of suicidal ideation and behavior have been reported in patients treated with AEDs in various indications, including epilepsy and bipolar disorder. In addition, a meta-analysis of randomized, placebo-controlled studies of AEDs (including lamotrigine) has shown a small increase in the risk of suicidal ideation and behavior. The mechanism of this risk is unknown, but the available data do not exclude the possibility of an increased risk for lamotrigine.

Therefore, patients should be monitored for any signs of suicidal ideation and behaviors. Patients (and their carers) should be advised to seek medical guidance if signs of suicidal ideation or behaviour arise.

Aggravation in Bipolar Disorder

Patients receiving ***LAMICTAL*** for the treatment of bipolar disorder should be closely monitored for any symptoms of clinical aggravation (including development of new symptoms) and suicidal risk, especially at the start of treatment, or at dosage changes. Some patients, such as those with a history of suicidal thinking or behavior, young adults, and those who have experienced significant suicidal ideation prior to initiating treatment, may be at increased risk for suicidal thoughts or attempts, and should be under careful monitoring during treatment.

Patients (and those caring for patients) should be alerted to the need to watch for any aggravation in their condition (including the presentation of new symptoms) and/or the presentation of ideas/behavior or thoughts of self-harm and that they should seek medical advice immediately upon such symptoms occurring.

The possibility of changing the therapeutic regimen, including the possibility of discontinuing medication, should be considered in those patients who experience clinical aggravation (including the presentation of new symptoms) and/or the presentation of suicidal ideation/behavior, particularly if those symptoms are severe, are of abrupt presentation, or are not part of the patient's previous symptomatology.

Hormonal contraceptives

Effects of Hormonal Contraceptives on the Efficacy of *LAMICTAL*

A combination of ethinyl estradiol/levonorgestrel (30 micrograms/150 micrograms) has been shown to increase the elimination of lamotrigine approximately twofold resulting in a decrease in lamotrigine levels (*see Interactions*). After adjustment, in most cases higher maintenance doses of lamotrigine (up to twice) will be necessary to achieve a maximal therapeutic response. In women not already taking a lamotrigine glucuronidation inducer 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 increases in the dose of lamotrigine are made in the days before or during the week of inactive medication. For dosing instructions see "General Dosage *Recommendations for* ***LAMICTAL*** *in Special Patient Populations, Dosage and Administration*".

Clinicians should make appropriate clinical management of women who initiate or discontinue hormonal contraceptives during ***LAMICTAL*** therapy and in most cases adjustments to the dose of lamotrigine will be necessary.

Other oral contraceptives and hormone replacement therapy (HRT) treatments have not been studied, although they may similarly affect the pharmacokinetic parameters of lamotrigine.

Effects of *LAMICTAL* on the Efficacy of Hormonal Contraceptives

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyl estradiol/levonorgestrel combination) are administered in combination, a modest increase in levonorgestrel clearance and changes in serum FSH and LH occur (*see Interactions*). The impact of these changes on the ovulatory activity of the ovaries is unknown. However, the possibility that these changes may result in decreased contraceptive efficacy in some patients taking hormonal formulations together with LAMICTAL cannot be excluded. Therefore, patients should be instructed to promptly report any changes in their menstrual pattern, e.g., advanced bleeding.

Effect of Lamotrigine on Organic Cation Transporter Substrates (OCT 2)

Lamotrigine is an inhibitor of renal tubular secretion by OCT 2 proteins (*see Interactions*). This can cause an elevation in plasma levels of certain drugs that are excreted mainly through this route. Co-administration of ***LAMICTAL*** with OCT 2 substrates with a narrow therapeutic index is not recommended, e.g., dofetilide is not recommended.

Dihydrofolate Reductase

Lamotrigine is a weak inhibitor of dihydrofolate reductase, therefore there is a possibility of interference with folate metabolism during long-term therapy. However, during prolonged dosing in humans, ***LAMICTAL*** did not induce significant changes in hemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations for up to 1 year or red blood cell folate concentrations for up to 5 years.

Kidney 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, therefore caution should be exercised when treating patients with renal failure.

Patients Taking Other Formulations Containing Lamotrigine

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

Brugada Pattern ECG

A very rare frequency association was observed with Brugada pattern ECG, although a causal relationship has not been established. Therefore, special attention should be paid before using ***LAMICTAL*** in patients with Brugada syndrome (see Pharmacodynamics)

Cardiac Rhythm and Conduction Abnormalities.

In vitro studies showed that LAMICTAL exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these in vitro findings, LAMICTAL could potentially slow ventricular conduction (widened QRS) and induce proarrhythmia in patients with clinically important structural or functional heart disease. Therefore, any expected or observed benefit of LAMICTAL for those patients should be carefully weighed against the potential risks of serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia (see Pharmacodynamics).

Epilepsy

As with other AEDs, abrupt withdrawal of ***LAMICTAL*** can lead to rebound crises. Unless safety concerns (e.g. rash) require abrupt withdrawal, the dose of ***LAMICTAL*** should be gradually decreased over a two-week period.

It has been reported in the literature that severe seizures including status epilepticus can lead to rhabdomyolysis, multiple organ dysfunction, and disseminated intravascular coagulation, sometimes with fatal outcomes. Similar cases associated with the use of ***LAMICTAL*** have occurred.

Bipolar disorder

Children and Adolescents (Under 18 Years of Age)

Treatment with antidepressant agents is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders.

Interactions

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for the metabolism of lamotrigine. Therefore, medicinal products that induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine. Strong or moderate inducers of cytochrome P450 enzyme 3A4 (CYP3A4), which are also known to induce UGTs, may increase lamotrigine metabolism. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine can induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

Those medicinal products that have been shown to have a clinically relevant effect on lamotrigine concentration are summarised in Table 6. In Dosage and Administration, a specific dosage guide is provided for these medications. In addition, this table lists those drugs that have been shown to have little or no effect on lamotrigine concentration. Co-administration of such medicinal products is generally not expected to have a clinical impact. However, patients whose epilepsy is particularly sensitive to fluctuations in lamotrigine concentrations should be considered.

Table 6: Effects of drugs on lamotrigine concentration

Drugs that increase the concentration of lamotrigine	Drugs that lower the level of lamotrigine	Drugs that have little or no effect on lamotrigine concentration
Valproate	Atazanavir/ritonavir Carbamazepine	Aripiprazole Bupropion Felbamate
	Ethinyl estradiol/levonorgestrel combination Lopinavir/ritonavir Phenobarbital Phenytoin Primidone Rifampicin*	Gabapentin Lacosamide Levetiracetam Lithium Olanzapine Oxcarbazepine Paracetamol Perampanel Pregabalin Topiramate Zonisamide

* For guidance on dosing, see Dosage and Administration — General Dosage Recommendations for ***LAMICTAL*** in Special Patient Populations, in addition to women taking hormonal contraceptives, see Warnings and Precautions - Hormonal Contraceptives.

Interactions Involving AEDs (*see Dosage and Administration*)

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and nearly doubles the average half-life of lamotrigine.

Certain AEDs (such as phenytoin, carbamazepine, phenobarbital and primidone) that induce cytochrome P450 enzymes also induce UGT, and consequently increase 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 observed during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

In a study of 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 in healthy volunteers, concomitant administration of felbamate (1200 mg twice daily) with ***LAMICTAL*** (100 mg twice daily for 10 days) appeared to have no clinically relevant effect on the pharmacokinetics of lamotrigine.

Based on a retrospective study of plasma levels in patients receiving ***LAMICTAL*** with and without gabapentin, gabapentin appears to have not changed the apparent clearance of lamotrigine.

Potential drug interactions between levetiracetam and lamotrigine were evaluated by determining serum concentrations of both agents during placebo-controlled clinical studies. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

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

Topiramate did not change plasma lamotrigine concentrations. Administration of ***LAMICTAL*** resulted in a 15% increase in topiramate concentrations.

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

Concomitant administration of lacosamide (200, 400 or 600 mg/day) did not affect plasma concentrations of lamotrigine in placebo-controlled clinical studies in patients with partial-onset seizures.

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

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

Interactions Involving Other Psychoactive Agents (*see Dosage and Administration*)

Coadministration of 100 mg/day of ***LAMICTAL*** did not alter the pharmacokinetics of lithium following 2 g of anhydrous lithium gluconate administered twice daily for six days to 20 healthy subjects.

Multiple oral doses of bupropion had no statistically significant effect on the pharmacokinetics of single doses of ***LAMICTAL*** in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

During a study with healthy adult volunteers, olanzapine 15 mg reduced lamotrigine AUC and $_{Cmax}$ by an average of 24% and 20%, respectively. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of ***LAMICTAL***, 400 mg daily, had no clinically significant effect on the pharmacokinetics of a single 2 mg dose of risperidone in 14 healthy adult volunteers. After concomitant administration of risperidone 2 mg with lamotrigine, 12 of the 14 volunteers reported somnolence, compared with 1 of 20 when risperidone alone was administered, and none when ***LAMICTAL*** was administered alone.

In a study in 18 adult patients with bipolar I disorder who received an established lamotrigine treatment regimen (>/=100 mg/day), aripiprazole doses were increased from 10 mg/day to a target of 30 mg/day over a 7-day period and continued once daily for an additional 7 days. An average reduction of approximately 10% in the Cmax and AUC of lamotrigine was observed.

In vitro inhibition experiments indicated that the formation of the major metabolite of lamotrigine, 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropon, clonazepam, fluoxetine, haloperidol, or lorazepam. Data on bufuralol metabolism of human liver microsomes suggest that lamotrigine does not reduce the elimination of drugs predominantly eliminated by CYP2D6. Results from in vitro experiments also suggest that the elimination of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives

Effect of Hormonal Contraceptives on the Pharmacokinetics of Lamotrigine

In a study of 16 volunteers, 30 micrograms of ethinyl estradiol/150 micrograms of levonorgestrel in a combined oral contraceptive pill caused an approximately twofold increase in oral lamotrigine elimination, producing an average reduction of 52% and 39% in lamotrigine AUC and Cmax, respectively. Serum concentrations of lamotrigine 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 on average being approximately twice as high as during co-therapy – *see Dosage and Administration – General Dosage Recommendations* for ***LAMICTAL*** *in Special Patient Populations* (for instructions for administration for women taking hormonal contraceptives) and *Warnings and Precautions – Hormonal Contraceptives*.

Effect of Lamotrigine on the Pharmacokinetics of Hormonal Contraceptives

In a study of 16 volunteers, a steady-state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyl estradiol component of a combined oral contraceptive pill. A modest increase in oral elimination of the

levonorgestrel component was observed, resulting in an average reduction of 19% and 12% in levonorgestrel AUC and Cmax, respectively. During the study, serum FSH, LH and estradiol measurements indicated some loss of ovarian hormone activity suppression in some women, although serum progesterone measurement indicated that there was no hormonal evidence of ovulation in any of the 16 patients. The impact of a modest increase in levonorgestrel elimination, and the change in serum FSH and LH, on ovarian ovulation activity is unknown (*see WARNINGS and PRECAUTIONS*). The effects of doses of lamotrigine other than 300 mg/day have not been studied and no studies have been conducted with other female hormonal formulations.

Interactions Involving Other Medications

In a study with 10 male volunteers, rifampicin increased the elimination of lamotrigine and decreased the half-life of lamotrigine due to the induction of liver enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the recommended treatment regimen for lamotrigine and concurrent glucuronidation inducers should be used (*see DOSAGE AND ADMINISTRATION*).

In a study of healthy volunteers, lopinavir/ritonavir approximately halved plasma lamotrigine concentrations, probably by inducing glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the recommended treatment regimen for lamotrigine and concurrent glucuronidation inducers should be used (*see DOSAGE AND ADMINISTRATION*).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and Cmax of lamotrigine (single dose 100 mg) by an average of 32% and 6%, respectively (*see DOSAGE AND ADMINISTRATION – General Dosing Recommendations for **LAMICTAL** in Special Patient Populations*).

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

Data from *the in vitro* evaluation of the effect of lamotrigine on OCT 2 demonstrate that lamotrigine, but not the glucuronide metabolite N(2), is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an OCT 2 inhibitor with a CI 50 value of 53.8 µM (*see Warnings and Precautions*).

Interactions Involving Laboratory Tests

LAMICTAL has been reported to interfere with rapid urine drug evaluation tests, which may result in false-positive readings, particularly for phencyclidine (PCP). More specific alternative chemical methods should be used to confirm a positive result.

Pregnancy and Lactation

Fertility

Administration of lamotrigine did not harm fertility in animal reproduction studies.

There is no experience with the effect of ***LAMICTAL*** on fertility in humans.

Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in more than 8700 women exposed to ***LAMICTAL*** monotherapy during the first trimester of pregnancy. Overall, these data do not suggest any evidence of substantial increases in the risk of major birth defects**.** Although data obtained from a limited number of registries have reported an increased risk of oral clefts in isolated cases. A completed case-control study demonstrated no increased risk of developing cleft palate compared with other major birth defects observed after exposure to lamotrigine (see Preclinical Information).

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

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 its therapeutic effect. Decreases in lamotrigine levels have been reported during pregnancy. Appropriate clinical management of pregnant women should be ensured during ***LAMICTAL*** therapy.

Nursing

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

The potential benefits of breastfeeding must be weighed against the potential risk of adverse effects that may occur in infants.

Effects on the Ability to Drive and Use Machinery

Two studies with volunteers have shown that the effect of ***LAMICTAL*** on fine visual motor coordination, eye movements, body swaying and subjective sedative effects does not differ from placebo. Neurological adverse events such as dizziness and diplopia have been reported in clinical trials with LAMICTAL. Therefore, patients should observe how ***LAMICTAL*** therapy affects them before driving or operating machinery.

Epilepsy

Since there are individual variations in response to all antiepileptic drug therapies, patients should consult with their physicians about specific driving problems and epilepsy.

Adverse Reactions

Adverse reactions of epilepsy or bipolar identified in clinical studies have been divided into specific sections by indication. Additional adverse reactions for both indications identified during postmarketing surveillance are included in the Postmarketing section. All three sections should be consulted when considering the overall safety profile of ***LAMICTAL.***

The following convention has been used for the classification of undesirable effects:- Very common (1/10), common (1/100 to< 1/10), uncommon (1/1000 to < 1/100), rare (1/10000 to< 1/1000), very rare (< 1/10000).>>>>

Epilepsy

The following adverse reactions were identified during clinical studies in epilepsy and should be considered in conjunction with those observed in the bipolar disorder and postmarketing clinical studies sections for an overall safety profile of ***LAMICTAL***.

Skin and Subcutaneous Tissue Disorders

Very commonExanthema.
RareStevens-Johnson syndrome.
Very rareToxic epidermal necrolysis

In aggregated, double-blind clinical trials in adults, rashes occurred in up to 10% of patients taking ***LAMICTAL*** and in 5% of patients taking placebo. Rashes led to withdrawal of ***LAMICTAL*** treatment in 2% of patients. The rash, usually maculopapular in appearance, usually appears within eight weeks of starting treatment and resolves when ***LAMICTAL*** is removed (*see Warnings and Precautions*).

Rarely, serious and potentially life-threatening rashes have been reported, including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome). Although most recovered upon withdrawal of the drug, some patients experienced irreversible scarring and rare cases of associated death have occurred. (*See Warnings and Precautions*.)

The overall risk of rash appears to be closely 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 drug reaction with Eosinophilia and Systemic Symptoms (DRESS); Also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms (*see Warnings and Precautions and Immune System Disorders***).

Blood and lymphatic system disorders

Very rarehematologic abnormalities including, neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, aplastic anemia, agranulocytosis), lymphadenopathy.

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

Immune System Disorders

Very rareDRESS/Hypersensitivity Syndrome** including symptoms such as fever, lymphadenopathy, facial edema, blood, liver, and kidney abnormalities.
Rash has also been reported as part of this syndrome showing a broad spectrum of clinical severity and can rarely lead to disseminated intravascular coagulation (DIC) and multiple organ failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even when rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately, and ***LAMICTAL* should be discontinued if no alternative etiology is established.

Psychiatric Disorders

Common: Aggressiveness, irritability.
Very rare: Tics, hallucinations, confusion.

Nervous System Disorders

Very commonHeadache.
CommonDrowsiness, insomnia, dizziness, tremor.
UncommonAtaxia.
RareNystagmus

Eye Disorders

UncommonDiplopia, blurred vision.

Gastrointestinal Disorders

CommonNausea, vomiting, diarrhea

Hepatobiliary disorders

Very rareIncreased liver function tests, liver dysfunction, liver failure

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

Musculoskeletal and Connective Tissue Disorders

Very rareLupus-like reactions

General Disorders and Conditions on the Administration Site

CommonTiredness

Bipolar disorder

The following adverse reactions identified during clinical studies in bipolar disorder should be considered in conjunction with those observed in the epilepsy and post-marketing clinical studies sections for an overall safety profile of ***LAMICTAL***.

Skin and Subcutaneous Tissue Disorders

Very commonExanthema.
RareStevens Johnson Syndrome

When considering all studies of bipolar disorder (controlled and uncontrolled) conducted with LAMICTAL, rashes occurred in 12% of patients with ***LAMICTAL***. While in controlled clinical trials with patients with bipolar disorder, rashes occurred in 8% of patients taking ***LAMICTAL*** and 6% of patients taking placebo.

NERVOUS system disorders

Very commonHeadache
CommonAgitation, drowsiness, dizziness.

Musculoskeletal and Connective Tissue Disorders

FrequentArthralgia.

General Disorders and Conditions on the Administration Site

CommonPain, back pain

Post-marketing

This section includes adverse reactions identified during postmarketing surveillance for both indications. The following adverse reactions should be considered in conjunction with those observed in the clinical studies in epilepsy and bipolar disorder sections for an overall safety profile of ***LAMICTAL***.

Blood and Lymphatic System Disorders

Very rareHemophagocytic lymphohistiocytosis (see WARNINGS and PRECAUTIONS)

Immune system disorders.

Very rarehypogammaglobulinemia

Skin and subcutaneous tissue disorders

RareAlopecia

Psychiatric disorders

Very rare: Nightmares.

Nervous system disorders

Very commonDrowsiness, ataxia, headache, dizziness.
Commonnystagmus, tremor, insomnia.
RareAseptic meningitis (see Warnings and Precautions).
Very rareAgitation, instability, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis.

LAMICTAL has been reported to worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye Disorders

Very commonDiplopia, blurred vision.
RareConjunctivitis.

Gastrointestinal Disorders

Very commonNausea, vomiting
CommonDiarrhea

Urinary and Renal Disorders

Very rareTubulointerstitial nephritis*
* May occur associated with uveitis.

Epilepsy only

Nervous System Disorders

Very rareIncreased frequency of seizures

Overdose

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose, including fatal cases, has been reported. Overdose can result in symptoms including nystagmus, ataxia, impaired consciousness, grand mal seizures and coma. QRS enlargement (intraventricular conduction delay) has also been observed in patients with overdose.

In the event of an overdose, the patient should be hospitalized and given appropriate supportive therapy. , as clinically indicated or recommended by national poison control centers, where available.

Pharmacological properties

Pharmacodynamics

ATC Code

N 03 AX 09

Mechanism of Action

The results of pharmacological studies suggest that lamotrigine is a voltage-gated gate-dependent sodium channel blocker. It produces a use- and voltage-dependent blockade of sustained repetitive firing in cultured neurons and inhibits the pathological release of glutamate (the amino acid that plays a key role in the generation of epileptic seizures), in addition to inhibiting the bursts of action potentials evoked by glutamate.

Pharmacodynamic effects

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

In tests designed to evaluate the effects of drugs on the central nervous system, results obtained using doses of 240 mg lamotrigine administered to healthy volunteers were not different from placebo, while 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, They increased body rocking and produced subjective sedative effects.

In another study, simple oral doses of 600 mg carbamazepine significantly impaired fine visual motor coordination and eye movements, while increasing both body roll and heart rate, while results with lamotrigine at doses of 150 mg and 300 mg were not different from placebo.

Pharmacokinetics

Absorption

Lamotrigine is rapidly and completely absorbed from the intestine without significant first-pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral administration of the drug. The time to peak concentration is slightly delayed after meals, but the extent of absorption is not affected. Pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable variation between individuals in peak steady-state concentrations, but in the same individual the concentration rarely varies.

Distribution

Plasma protein binding is close to 55%; A displacement of plasma proteins is very unlikely to 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 the metabolism of lamotrigine.

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

Elimination

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

The half-life of lamotrigine is greatly affected by concomitant medicinal products. The average half-life is reduced to approximately 14 hours when administered with glucuronidation-inducing drugs such as carbamazepine and phenytoin, and increases to a median of approximately 70 hours when coadministered with valproate alone (*see Dosage and Administration and Interactions*).

Special Patient Populations

Children

Elimination adjusted for body weight is higher in children than in adults, with the highest values occurring in children under five years of age. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when administered with enzyme-inducing drugs such as carbamazepine and phenytoin and increases to mean values of 45 to 50 hours when coadministered with valproate alone. (*See Dosage and Administration*.)

Elderly

The results of a population pharmacokinetic analysis, including both young and elderly patients with epilepsy, recruited in the same tests, indicated that the elimination of lamotrigine did not change to a clinically relevant point. After single doses, apparent elimination decreased by 12% from 35 mL/min at age 20 and to 31 mL/min at age 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min among the young and elderly groups. In addition, the pharmacokinetics of lamotrigine were studied in 12 healthy elderly subjects following a single dose of 150 mg. Mean elimination in the elderly (0.39 mL/min/kg) is within the range of mean elimination 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 Insufficiency

Twelve volunteers with chronic renal failure and 6 other individuals undergoing hemodialysis each received a single 100 mg dose of lamotrigine. The mean CL/F was 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. The mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between hemodialysis) and 13.0 hours (during hemodialysis), 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 removed during a 4-hour hemodialysis session. For this patient population, initial doses of ***LAMICTAL*** should be based on the patients' AED regimen; a maintenance dose reduction may be effective for patients with significant impairment of renal function.

Patients with Hepatic Insufficiency

A single-dose pharmacokinetic study was conducted in 24 subjects with varying degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent elimination of lamotrigine was 0.31, 0.24, or 0.10 mL/min/kg in patients with Grade A, B, or C hepatic impairment (Child - Pugh classification), respectively, compared with 0.34 mL/min/kg in healthy controls. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate hepatic impairment (Child-Pugh Grade B) and 75% in patients with severe hepatic impairment (Child-Pugh Grade C). Escalation and maintenance doses should be adjusted according to clinical response.

Clinical studies

Clinical Safety and Efficacy Profiles of Adjuvant Therapy in Patients 1–24 Months of Age with Partial Seizures

A multicenter, double-blind, placebo-controlled additive study (Study LAM20006) evaluated the efficacy of lamotrigine administered as adjuvant therapy in patients 1 to 24 months of age with partial seizures. Lamotrigine was added to 1 or 2 AEDs during an open-label phase (n=177).

Lamotrigine was administered every other day or once daily if a total starting dose or dose adjustment of less than 2 mg was required. Serum levels were quantified at the end of week 2 of the titration period; the subsequent dose was reduced or not increased if the concentration exceeded 0.41 ug/mL of the expected concentration in adults at this time point. In some patients, dose reductions of up to 90% were required by the end of week 2. If valproate was used as an AED, lamotrigine was added only after valproate therapy had been given to the infant for 6 months without abnormal liver function test results. The safety and efficacy profiles of lamotrigine in patients with body weights less than 6.7 kg, and who are taking valproate or any AED other than carbamazepine, phenytoin, phenobarbital or primidone have not yet been evaluated.

Patients who achieved a 40% or greater reduction in the incidence frequency of partial seizures (n=38) were randomized to either gradual withdrawal from placebo (n=19) or continuation of lamotrigine therapy (n=19) for up to 8 weeks. The main measure of effectiveness was based on the difference in the proportion of subjects receiving lamotrigine or placebo who met the defined escape criteria. The escape criteria allowed for the withdrawal of subjects from the study, if their epilepsy conditions showed any signs of clinical deterioration. No statistical significance was reached on the primary endpoint; However, fewer patients met the escape criteria in the lamotrigine group (58%), compared to the placebo group (84%), and it took them longer to meet the escape criteria (42 versus 22 days).

The adverse event profile was similar to that observed in older children.

Clinical Efficacy in the Prevention of Depressive Episodes in Patients with Bipolar Disorder

Adults (18 Years of Age and Older)

Two pivotal studies have demonstrated efficacy in preventing depressive episodes in patients with bipolar I disorder.

The SCAB20003 clinical study was a multicenter, double-blind, double-sham, placebo- and lithium-controlled, fixed-dose, randomized evaluation of long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who recently experienced or were currently experiencing a major depressive episode. Once stabilized using LAMICTAL or LAMICTAL monotherapy plus psychotropic medications, patients were randomly assigned to one of five treatment groups: ***LAMICTAL*** (50, 200, 400 mg/day), lithium (serum levels 0.8 to 1.1 mMol/L), or placebo for up to 76 weeks (18 months). Treatment regimens were maintained until an episode of emerging mood (depressive or manic) necessitated intervention with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where interventions were additional pharmacotherapy or ECT. We analyzed this endpoint using three methods for handling data from patients who withdrew before having an intervention. The p-values for these analyses ranged from 0.003 to 0.029. In supporting analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, ***LAMICTAL*** patients had longer times to first depressive episode than placebo patients (p=0.047), and the difference between treatment with respect to time to a manic/hypomanic or mixed episode was not statistically significant.

The SCAB2006 clinical study was a multicenter, double-blind, double-sham, placebo- and lithium-controlled, randomized, flexible-dose evaluation of ***LAMICTAL*** in the long-term prevention of relapse and recurrence of mania and/or depression in patients with bipolar I disorder who recently experienced or were currently experiencing a manic or hypomanic episode. Once stabilized using LAMICTAL or LAMICTAL monotherapy plus psychotropic medications, patients were randomly assigned to one of three treatment groups: ***LAMICTAL*** (100 to 400 mg/day),

lithium (serum levels 0.8 to 1.1 mMol/L), or placebo for up to 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) necessitated intervention with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where interventions were additional pharmacotherapy or ECT. This endpoint was analyzed using three methods of handling data from patients who withdrew before having an intervention. The p-values for these analyses were in the range of 0.003 to 0.023. In supporting analyses of time to first episode of depression and time to first manic/hypomanic or mixed episode, patients with ***LAMICTAL*** had longer times to first depressive episode than patients on placebo (p=0.015), and the difference between treatment with respect to manic/hypomanic or mixed episodes was not statistically significant.

In clinical trials, the propensity to induce destabilization, mania, or hypomania during ***LAMICTAL*** therapy was not significantly different from placebo.

Preclinical Information

Studies of lamotrigine on reproductive toxicology in animals, at doses lower than the therapeutic human dose of 400 mg/day [based on body surface area (mg/m2)] showed developmental toxicity (increased mortality, decreased body weight, increased structural variations, neurological behavior abnormalities), but without teratogenic effects. However, since lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of malformations in the human fetus when the mother is being treated with a folate inhibitor during pregnancy.

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

Lamotrigine was not carcinogenic in long-term studies in rats and mice.

Pharmaceutical Information

List of Excipients

Tablets

Lactose

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Iron oxide yellow (E172)

Magnesium stearate

Dispersible/chewable tablets

Calcium carbonate

Low substitution hydroxypropyl cellulose

Magnesium aluminium silicate

Sodium starch glycolate

Povidone

Sodium saccharin

Blackcurrant flavor

Magnesium stearate

Shelf Life

The expiration date is indicated on the packaging.

Storage

Storage conditions are detailed on the packaging. Special Precautions for Storage

Keep dry.

Protect dispersible/chewable tablets from light.

Nature and Content of the Container

Tablets

LAMICTAL 25 mg is available in PVC/aluminium blister or child-resistant PVC/aluminium blister.

LAMICTAL 50 mg, 100 mg and 200 mg are available in PVC/aluminium blister or PVC/aluminium/childproof paper blister.

Dispersible/chewable tablets

LAMICTAL 2 mg is available in child-proof/tamper-proof HDPE bottles.

LAMICTAL 5 mg is available in PVC/PVdC/aluminium blister packs or HDPE bottles with continuous child/tamper proof screw closure.

LAMICTAL 25 mg, 50 mg, 100 mg and 200 mg are available in PVC/PVdC/aluminium blister packs or PVC/PVdC/aluminium/childproof paper blister packs

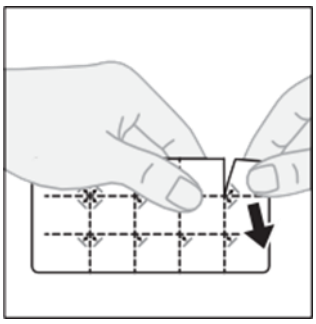
Incompatibilities

No reports

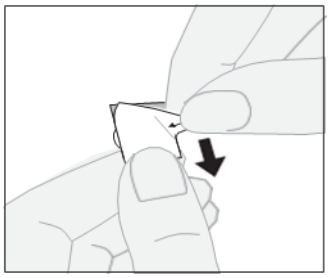
Use and Management

The 25 mg, 50 mg, 100 mg and 200 mg dispersible/chewable tablets can be supplied with a child-resistant peelable opening function.

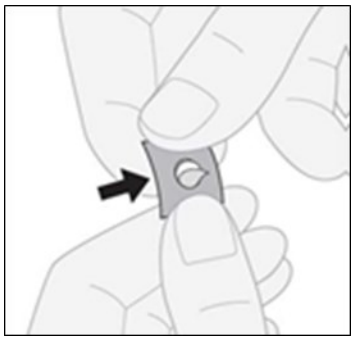
1. Separate a tablet: Tear along the cutting lines to separate a "pocket" from the blister.



2. Peel off the outer layer: starting at the corner, lift and peel over the pocket.



3. Push the tablet: Gently push one end of the tablet through the aluminum layer.



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