

Arrow - Lamotrigine

Lamotrigine 2 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg dispersible/chewable tablets

Presentation

Arrow - Lamotrigine 2 mg White to off-white, round tablets embossed with 'LI' over '2' on one side and 'S' on the other side

Arrow - Lamotrigine 5 mg White to off-white, oval tablet, embossed with 'LI' scoreline '5' on one side and 'S' on the other side

Arrow - Lamotrigine 25 mg White to off-white, shield-shaped tablet, embossed with 'S' over 'LI25' on one side and a scoreline on the other side

Arrow - Lamotrigine 50 mg White to off-white, shield-shaped tablet, embossed with 'S' over 'LI50' on one side and a scoreline on the other side

Arrow - Lamotrigine 100 mg White to off-white, shield-shaped tablet, embossed with 'S' over 'LI100' on one side and a scoreline on the other side

Arrow - Lamotrigine 200 mg White to off-white, shield-shaped tablet, embossed with 'S' over 'LI200' on one side and a scoreline on the other side

Uses

Actions

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

Pharmacodynamics

In tests designed to evaluate the central nervous system (CNS) effects of medicines, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from placebo, whereas both 1,000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, increased body sway and produced subjective sedative effects.

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

Clinical trials

EPILEPSY

Adult add-on treatment of partial and generalised seizures

The efficacy and safety of lamotrigine have been demonstrated in six double-blind, placebo controlled, crossover studies (n = 221) with duration of lamotrigine treatment ranging from 8 to 12 weeks, using doses up to 400 mg. Additionally, a double-blind, placebo controlled, parallel study was performed of two fixed doses of lamotrigine (300 mg, n = 71; 500 mg, n = 72) versus placebo (n = 73). The median percentage reduction in total seizure count on lamotrigine compared to placebo significantly favoured lamotrigine in five of the six crossover trials. Overall 23% (range 7 to 67%) of patients in the controlled crossover trials showed a greater than or equal to 50% reduction in total seizures in lamotrigine compared to placebo. In the controlled parallel study the median reduction (%) from baseline in total seizures during weeks 13 to 24 was 14% on placebo compared to 23% on lamotrigine 300 mg and 32% on lamotrigine 500 mg. The difference from placebo was statistically significant for lamotrigine 500 mg but not for lamotrigine 300 mg. The most common adverse experiences affected the CNS (ataxia, dizziness, diplopia) and occurred more frequently on lamotrigine 500 mg than lamotrigine 300 mg in the controlled parallel study. Across the controlled trials, approximately 10% of patients on lamotrigine developed a rash compared to 5% on placebo, with approximately 3% of patients on lamotrigine withdrawing with this adverse experience.

Adult monotherapy

Two 48-week, double-blind, randomised, active controlled (carbamazepine and phenytoin, respectively) clinical trials of lamotrigine monotherapy in the treatment of newly diagnosed epilepsy have been conducted. An additional randomised, active controlled (carbamazepine), open trial in this patient population has also been conducted. A total of 784 patients from these three studies were analysed (443 lamotrigine, 246 carbamazepine and 95 phenytoin). These studies indicate that the efficacy of lamotrigine monotherapy, in both generalised and partial seizures, may be comparable to that seen with carbamazepine and phenytoin. The escalation dose of lamotrigine in these studies that was associated with the lowest incidence of rash leading to withdrawal (2.2%) was 25 mg daily for the first 2 weeks, followed by 50 mg daily for the next 2 weeks, to achieve a maintenance dose of 100 to 200 mg/day by weeks 5 to 6 (see **Adverse Effects** and **Interactions**).

Paediatric add-on therapy

The safety and efficacy of lamotrigine have been demonstrated in 285 children with refractory epilepsy aged 2 to 12 years in five open add-on trials of 48 weeks duration. Lamotrigine appeared effective in both partial and generalised seizure types. Across all seizure types, 34% of patients experienced greater than or equal to 50% reduction in seizures. The modal maintenance dose was 5 to 15 mg/kg for those not taking valproate and 1 to 5 mg/kg for those taking valproate. 7% of patients discontinued lamotrigine due to skin rash. In patients on concomitant valproate, 2% withdrew after a rash

when their daily dose of lamotrigine in the first week of treatment was less than or equal to 0.5 mg/kg compared to 13% withdrawn with rash at an initial dose of lamotrigine greater than 0.5 mg/kg. 155 patients aged 2 to 18 years (123 patients aged 12 years or under) continued to receive lamotrigine for up to 4 years. 4% of these patients withdrew because of adverse experiences. Lamotrigine had no effect on expected normal weight and height increases when taken for periods of up to 4 years.

Lennox-Gastaut syndrome

Lamotrigine may be of benefit as add-on therapy for seizures associated with Lennox-Gastaut syndrome. One double-blind, placebo controlled, add-on, parallel study has been performed in patients aged 3 to 25 years with Lennox-Gastaut syndrome. These patients were being treated with a combination of up to three anti-epileptic drugs including carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, lorazepam, nitrazepam, oxcarbazepine, phenobarbitone, primidone, phenytoin, sodium valproate or vigabatrin. There is no data available on the use of lamotrigine as the sole drug treatment of Lennox-Gastaut syndrome. No single drug is likely to be of benefit.

After a 4-week run-in period, patients (2 to 28 years old) were randomised to receive either lamotrigine (n = 79; 3 to 25 years old) or placebo (n = 90) for 16 weeks (including dose escalation period in the first 6 weeks of treatment) in addition to their existing therapy. Addition of lamotrigine to existing therapy resulted in a median reduction in counts of major motor seizures (drop attacks and tonic-clonic seizures) of 32% compared to a reduction of 9% in patients on existing therapy with add-on placebo. The results were also significantly in favour of lamotrigine when drop attacks and generalised tonic-clonic seizures were analysed separately, but not for atypical absence seizures. Rash was recorded in 7/79 lamotrigine add-on patients versus 4/90 placebo add-on patients. 4% of add-on lamotrigine patients and 8% of add-on placebo patients were withdrawn because of adverse experiences. 3% discontinued lamotrigine due to rash compared to 1% on placebo. In the lamotrigine group, one patient was hospitalised because of rash and a second was reported to have developed Stevens-Johnson syndrome but did not require hospitalisation. Worsening seizures caused 4% of patients on placebo to withdraw from treatment but none in and no patients on lamotrigine.

BIPOLAR DEPRESSION

Prevention of depressive episodes in patients with bipolar disorder

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

Clinical study SCAB20003 was a multicentre, double-blind, double-dummy, placebo and lithium controlled, randomised **fixed** dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who recently had or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200,

400 mg/day), lithium (serum levels of 0.8 to 1.1 mEq/L) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

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

Clinical study SCAB2006 was a multicentre, double-blind, double-dummy, placebo and lithium controlled, randomised **flexible** dose evaluation of lamotrigine in the long-term prevention of relapse and recurrence of manic and/or depression in patients with bipolar I disorder who recently had or were currently experiencing a manic or hypomanic episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of three treatment groups: lamotrigine (100 to 400 mg/day), lithium (serum levels of 0.8 to 1.1 mEq/L) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or ECT.

The primary endpoint was TIME, where the interventions were either additional pharmacotherapy or ECT. This endpoint was analyzed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p values for these analyses ranged from 0.003 to 0.023. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine patients had longer times to first depressive episode than placebo patients ($p = 0.015$), and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on lamotrigine therapy was not significantly different to 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. Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers, there is a modest induction of its own metabolism. However, there is no evidence that lamotrigine affects the pharmacokinetics of other anti-epileptic drugs. Also, data suggests that interactions between lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur.

94% of a radiolabelled dose of lamotrigine given to human volunteers was recovered in the urine over a period of 168 hours. Only 2% was recovered in the faeces. Lamotrigine is extensively metabolised in humans and the major metabolite is an N-glucuronide, which accounts for 65% of the dose recovered in the urine. A further 8% of the dose is recovered in the urine as unchanged lamotrigine. High performance liquid chromatography radiodetection revealed the presence of another N-glucuronide metabolite present at about one-tenth of the concentration of the major metabolite.

Elimination

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

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

Special populations

Children (12 years or under)

Clearance adjusted for bodyweight is higher in children (aged 12 years or under) than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults, with a mean value of approximately 7 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin, and increasing to mean values of 45

to 50 hours when co-administered with valproate alone (see Dosage and Administration).

Elderly (65 to 76 years)

Results of a population pharmacokinetic analysis including both young and elderly (65 to 76 years) patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses, apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups.

In addition, the pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39 mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) that were obtained in nine studies with non-elderly adults after single doses of 30 to 450 mg.

Renal impairment

Twelve volunteers with chronic renal failure and another 6 individuals undergoing haemodialysis were each given a single dose of 100 mg lamotrigine. Mean CL/F were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis), and 1.57 mL/min/kg (during haemodialysis) compared to 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on patients' anti-epileptic drug regimen, and reduced maintenance doses may be effective for patients with significant renal functional impairment.

Hepatic impairment

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

Indications

EPILEPSY

Adults and children over 12 years of age

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

Children (2 to 12 years of age)

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

BIPOLAR DISORDER (adults 18 years of age and over)

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

Dosage and Administration

Arrow - Lamotrigine Tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with water.

If a calculated dose of lamotrigine (e.g. for use in children with epilepsy or patients with hepatic impairment) does not equate to whole tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

Re-starting therapy

Prescribers should assess the need for escalation to maintenance dose when re-starting lamotrigine in patients who have discontinued lamotrigine for any reason, as there is a risk of serious rash 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 (see **Pharmacokinetics**), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule.

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

EPILEPSY

Add-on therapy

Adults and children over 12 years of age

In patients taking valproate with/without any other anti-epileptic drug, 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 to 50 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or in two divided doses.

In those patients taking concomitant anti-epileptic drugs or other medications (see **Interactions**) that induce lamotrigine glucuronidation with/without other anti-epileptic drugs (except valproate), the initial lamotrigine dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 to 400 mg/day, given in two divided doses.

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

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see **Interactions**), 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 to 100 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Table 1 Add-on therapy in epilepsy for adults and children over 12 years

Treatment regimen	Weeks 1 and 2	Weeks 3 and 4	Maintenance dose
Add-on therapy with valproate, regardless of any concomitant medications	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once daily)	100 - 200 mg/day (once daily or two divided doses) To achieve maintenance, doses may be increased by 25 - 50 mg every 1 - 2 weeks
Add-on therapy without valproate			

This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see Interactions)	50 mg/day (once daily)	100 mg/day (two divided doses)	200 - 400 mg/day (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1 - 2 weeks
This regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	25 mg/day (once daily)	50 mg/day (once daily)	100 - 200 mg/day (once daily or two divided doses) To achieve maintenance, doses may be increased by 50 - 100 mg every 1 - 2 weeks
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see Interactions), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

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

Children (2 to 12 years of age)

In patients taking valproate with/without any other anti-epileptic drugs, the initial lamotrigine dose is 0.15 mg/kg bodyweight/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 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 5 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

In those patients taking concomitant anti-epileptic drugs or other medications (see **Interactions**) that induce lamotrigine glucuronidation with/without other anti-epileptic drugs (except valproate), the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for 2 weeks, followed by 1.2 mg/kg/day given in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5 to 15 mg/kg/day, given in two divided doses, with a maximum of 400 mg/day.

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see **Interactions**), the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for 2 weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day, given once a day or in two divided doses, with a maximum of 200 mg/day.

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

Table 2 Add-on therapy in epilepsy for children aged 2 to 12 years

Treatment regimen	Weeks 1 and 2	Weeks 3 and 4	Maintenance dose
Add-on therapy with valproate , regardless of any concomitant medications	0.15 mg/kg* (once daily)	0.3 mg/kg (once daily)	0.3 mg/kg increments every 1 - 2 weeks to achieve a maintenance dose of 1 - 5 mg/kg (once daily or two divided doses) to a maximum of 200 mg/day
Add-on therapy without valproate			
This regimen should be used with: - phenytoin - carbamazepine - phenobarbitone - primidone or - other inducers of lamotrigine glucuronidation (see Interactions)	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	1.2 mg/kg increments every 1 - 2 weeks to achieve a maintenance dose of 5 - 15 mg/kg (once daily or two divided doses) to a maximum of 400 mg/day
This regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every 1 - 2 weeks to achieve a maintenance dose of 1 - 10 mg/kg (once daily or two divided doses) to a maximum of 200 mg/day
NOTES: (1) In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see Interactions), the treatment regimen as recommended for lamotrigine with concurrent valproate			

should be used.

(2) If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first 2 weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

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

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

Children aged less than 2 years

There is insufficient information on the use of lamotrigine in children aged less than 2 years.

When other anti-epileptic drugs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect that may have on lamotrigine pharmacokinetics (see Interactions). Whether or not optimal dosing has been achieved, a re-evaluation of all anti-epileptic drugs in the regime should be considered if a change or no improvement in seizure control or an appearance or worsening of adverse experiences is observed.

Withdrawal of concomitant anti-epileptic drugs

The dose of lamotrigine following the withdrawal of concomitant anti-epileptic drugs will be dependent upon the pharmacokinetics of the drug(s) being withdrawn, together with the overall clinical response of the patient. The withdrawal of enzyme inducing anti-epileptic drugs (e.g. phenytoin and carbamazepine) may not require a reduction in the lamotrigine dose unless there is a need due to safety considerations. However, an increase in the lamotrigine dose may be required following the withdrawal of enzyme inhibiting anti-epileptic drugs like sodium valproate (see Warnings and Precautions, and Interactions).

Discontinuation of lamotrigine in patients with epilepsy

As with other anti-epileptic drugs, abrupt withdrawal of lamotrigine may provoke rebound seizures and should be avoided wherever possible. Unless safety concerns (e.g. serious skin reactions) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

BIPOLAR DISORDER

Adults (18 years of age and over)

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

Lamotrigine is recommended for use in bipolar patients at risk for a future depressive episode. The following transition regimen should be followed to prevent recurrence of depressive episodes. This regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over 6 weeks after

which other psychotropic drugs and/or anti-epileptic drugs can be withdrawn, if clinically indicated.

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

Table 3 Treatment regimen in bipolar depression for adults 18 years and over

Treatment regimen	Weeks 1 and 2	Weeks 3 and 4	Week 5	Target stabilisation dose - week 6*
a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once daily)	50 mg/day (once daily or two divided doses)	100 mg/day (once a day or two divided doses) (maximum 200 mg daily)
b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see Interactions)	50 mg/day (once daily)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6 If necessary, increasing to 400 mg/day in week 7 (two divided doses)
c) Adjunct therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions) or Monotherapy with lamotrigine	25 mg/day (once daily)	50 mg/day (once daily or two divided doses)	100 mg/day (once daily or two divided doses)	200 mg/day (range 100 - 400 mg) (once daily or two divided doses)

NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see **Interactions**), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

* Depending on clinical response, the target stabilisation dose will alter.

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

In patients taking glucuronidation inhibiting concomitant drugs such as valproate, the initial lamotrigine dose is 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 weeks. The dose should be increased to 50 mg once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day, given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.

b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate (this regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce lamotrigine glucuronidation; see Interactions)

In those patients taking drugs that induce lamotrigine glucuronidation and NOT taking valproate, the initial lamotrigine dose is 50 mg given once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. The dose should be increased to 200 mg/day, given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day. However, the usual target dose to achieve optimal response is 400 mg/day, given in two divided doses, which may be given from week 7.

c) Adjunct therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see Interactions)

The initial lamotrigine dose is 25 mg once a day for 2 weeks, followed by 50 mg once a day (or in two divided doses) for 2 weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day, given once a day or as two divided doses. However, a range of 100 to 400 mg was used in clinical trials.

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule below.

Table 4 Maintenance stabilisation total daily dose in bipolar depression following the withdrawal of concomitant psychotropic or anti-epileptic drugs

Treatment regimen	Week 1	Week 2	Week 3 onwards*
a) Following withdrawal of inhibitors of lamotrigine glucuronidation e.g. valproate	Double the stabilisation dose, not exceeding 100 mg/week i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day	200 mg/day (two divided doses)	200 mg/day (two divided doses)
b) Following withdrawal of inducers of lamotrigine glucuronidation, depending on original dose This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see Interactions)	400 mg/day	300 mg/day	200 mg/day
	300 mg/day	225 mg/day	150 mg/day
	200 mg/day	150 mg/day	100 mg/day
c) Following withdrawal of other drugs that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)	Maintain target dose achieved in dose escalation (i.e. 200 mg/day in two divided doses; range 100 - 400mg)		
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see Interactions), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.			

* Dose may be increased to 400 mg/day as needed.

a) Following withdrawal of adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate

The dose of lamotrigine should be increased to double the original target stabilisation dose and maintained at this, once valproate has been terminated.

b) Following withdrawal of adjunct therapy with inducers of lamotrigine glucuronidation, depending on original maintenance dose (this regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce lamotrigine glucuronidation; see Interactions)

The dose of lamotrigine should be gradually reduced over 3 weeks as the glucuronidation inducer is withdrawn.

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

The target dose achieved in the dose escalation program should be maintained throughout withdrawal of the other medications.

There is no clinical experience in adjusting the lamotrigine daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made.

Table 5 Adjustment of lamotrigine daily dosing in patients with bipolar depression following addition of other medications

Treatment regimen	Current lamotrigine stabilisation dose	Week 1	Week 2	Week 3 onwards
Addition of inhibitors of lamotrigine glucuronidation e.g. valproate, depending on original dose of lamotrigine	200 mg/day	100 mg/day	100 mg/day	100 mg/day
	300 mg/day	150 mg/day	150 mg/day	150 mg/day
	400 mg/day	200 mg/day	200 mg/day	200 mg/day
Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate and depending on original dose of lamotrigine This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see Interactions)	200 mg/day	200 mg/day	300 mg/day	400 mg/day
	150 mg/day	150 mg/day	225 mg/day	300 mg/day
	100 mg/day	100 mg/day	150 mg/day	200 mg/day
Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see	Maintain target dose achieved in dose escalation (i.e. 200 mg/day; range 100 - 400 mg)			

Interactions)	
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see Interactions), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.	

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 step-wise reduction of dose.

Children and adolescents (less than 18 years of age)

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

General dosing recommendations in epilepsy and bipolar depression

Special patient populations

Women taking hormonal contraceptives

(a) Starting lamotrigine in patients already taking hormonal contraceptives

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see **Warnings and Precautions**, and **Interactions**), no adjustments to the recommended dose escalation guidelines for 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 e.g. valproate; whether lamotrigine is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbitone, primidone, rifampicin or lopinavir/ritonavir; or whether lamotrigine is added in the absence of valproate, carbamazepine, phenytoin, phenobarbitone, primidone, rifampicin or lopinavir/ritonavir (see Table 1 for epilepsy and Table 3 for bipolar depression).

(b) 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 two-fold according to the individual clinical response (see **Warnings and Precautions**, and **Interactions**).

(c) Stopping 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 decreased by as much as 50% according to the individual clinical response (see Warnings and Precautions, and Interactions).

Elderly (over 65 years)

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

Hepatic impairment

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

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' anti-epileptic drug regimen. Reduced maintenance doses may be effective for patients with significant renal functional impairment (see **Warnings and Precautions**, and **Pharmacokinetics - Special populations**).

Contraindications

Arrow - Lamotrigine is contraindicated in individuals with known hypersensitivity to lamotrigine or any component of this preparation (see **Further Information**).

Warnings and Precautions

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first 8 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 include potentially life-threatening rashes such as Stevens-Johnson syndrome and toxic epidermal necrolysis (see **Adverse Effects**).

In adults enrolled in studies utilizing the current lamotrigine dosing recommendations, the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as Stevens-Johnson syndrome (1 in 1,000).

In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1,000.

The risk of serious skin rashes in children is higher than in adults. Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in epileptic children is from 1 in 300 to 1 in 100. In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first 8 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 (see **Dosage and Administration**);
- concomitant use of valproate (see **Dosage and Administration**).

Caution is also required when treating patients with a history of allergy or rash to other anti-epileptic drugs as 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 from lamotrigine immediately unless the rash is clearly not drug-related. It is recommended that lamotrigine should not be re-started in patients who have discontinued the therapy due to rash unless the potential benefit clearly outweighs the risk (see **Dosage and Administration - Re-starting therapy**).

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver (see **Adverse Effects**). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though the 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.

Risk of suicidality

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy, as well as psychiatric disorders and other conditions, revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo

(0.22%). The increased risk of suicidal behaviour and/or ideation was observed as early as 1 week after starting the anti-epileptic drug and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. Such risk is considered to be a class effect of anti-epileptic drugs. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

Patients who are currently taking or starting on any anti-epileptic drugs should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour, or depression, especially if these symptoms are severe, abrupt in onset, or were not part of the patients' presenting symptoms. 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.

Health care professionals should inform patients, their families and caregivers of the potential for an increase risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

In children and adolescents (less than 18 years of age) with major depressive disorder and other psychiatric disorders, treatment with antidepressants has also been reported to associate with an increased risk of suicidal thinking and behaviour.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

An ethinylloestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see **Interactions**). Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes 1 week of inactive medication (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive medication. For dosing instructions, see **General dosing recommendations - Women taking hormonal contraceptives**.

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

Other oral contraceptives and hormone therapies have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see **General dosing recommendations - Women taking hormonal contraceptives**, and **Warnings and Precautions**).

Effects of lamotrigine on hormonal contraceptive efficacy

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinylloestradiol/levonorgestrel combination) were co-administered, there was a modest increase in levonorgestrel clearance and changes in serum follicle-stimulating hormone (FSH) and luteinising hormone (LH; see **Interactions**). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine is a weak inhibitor of dihydrofolate reductase and, 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 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.

Other preparations containing lamotrigine

Arrow - Lamotrigine should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

Drug withdrawal

As with other anti-epileptic drugs, abrupt withdrawal of lamotrigine may provoke rebound seizures. Unless safety concerns (e.g. rash) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

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

Severe convulsive seizures

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

Fertility

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

Use in pregnancy (Category D)

Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Post-marketing data from several prospective pregnancy registries have documented outcomes in over 2,000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. The North American Antiepileptic Drug Pregnancy (NAAED) registry has reported a marked and statistically significant increase in the rate of isolated oral cleft malformations. The observed prevalence of oral clefts was 24-fold higher than in the Brigham and Women's Hospital (BWH) birth malformation surveillance program, the reference population for the registry. Overall, the NAAED registry identified five cases of oral clefts in 564 exposed women, giving a prevalence rate of 8.9/1,000.

In a pooled analysis of other pregnancy registries, the rate of isolated oral clefts with lamotrigine monotherapy was 4 in 2,226, giving a prevalence rate of 1.79/1,000. This prevalence is at the upper end of, but does not exceed, the rates for general population prevalence reported in the literature.

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

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during lamotrigine therapy should be ensured.

Teratogenicity

Reproductive toxicology studies with lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects. However, as lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

Use in lactation

There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that lamotrigine passes into breast milk in concentrations usually of the order of 40 to 60% of the serum concentration.

In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur.

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

Pre-clinical safety data

The results of a wide range of mutagenicity tests indicate that lamotrigine does not present a genetic risk to man. Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

Effects on ability to drive or use machinery

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine, adverse events 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.

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

Adverse Effects

Based on the data available, the undesirable effects have been divided into sections for epilepsy and bipolar disorder from clinical studies, and post-marketing experience. However, these three sections should be consulted when considering the overall safety profile of lamotrigine.

The following convention has been utilised for the classification of undesirable effects: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1,000$), very rare ($< 1/10,000$).

EPILEPSY

Skin and subcutaneous tissue disorders

Very common: skin rash

Rare: Stevens-Johnson syndrome

Very rare: toxic epidermal necrolysis

In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% of patients taking placebo. The skin

rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within 8 weeks of starting treatment and resolves on withdrawal of lamotrigine (see **Warnings and Precautions**).

Rarely, serious potentially life threatening skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported. Although the majority recovers on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see **Warnings and Precautions**).

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

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

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see **Immune system disorders** in this section).

Blood and lymphatic system disorders

Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis

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

Immune system disorders

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

* Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to DIC and multi-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 such signs and symptoms are present, the patient should be evaluated immediately and withdrawn from lamotrigine discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common: irritability

Uncommon: aggression

Very rare: tics, hallucinations, confusion

In clinical studies, patients treated with lamotrigine were found to be at increased risk for suicidality when compared to placebo, the symptoms of

which included suicidal behaviour, suicidal ideation and emergence or worsening of existing depression (see **Warnings and Precautions**).

Nervous system disorders

Very common: headache, dizziness

Common: nystagmus, tremor, ataxia, drowsiness, insomnia

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

There have been reports that lamotrigine may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders

Very common: diplopia, blurred vision

Rare: conjunctivitis

Gastrointestinal disorders

Common: gastrointestinal disturbance (including vomiting and diarrhoea)

Hepato-biliary disorders

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

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

Musculoskeletal and connective tissue disorders

Very rare: lupus-like reactions

General disorders

Common: tiredness

BIPOLAR DISORDER

The adverse effects below, which were observed during the bipolar disorder clinical trials, should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

Skin and subcutaneous tissue disorders

Very common: skin rash

Rare: Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 14% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 9% of patients taking lamotrigine and in 8% of patients taking placebo.

Nervous system disorders

Very common: headache

Common: agitation, somnolence, dizziness

Psychiatric disorders

In clinical studies, patients treated with lamotrigine were found to be at increased risk for suicidality when compared to placebo, the symptoms of which included suicidal behaviour, suicidal ideation and emergence or worsening of existing depression (see **Warnings and Precautions**).

Musculoskeletal and connective tissue disorders

Common: arthralgia

General disorders

Common: pain, back pain

POST-MARKETING EXPERIENCE

The incidence of adverse reactions to lamotrigine is difficult to reliably assess due to the nature of spontaneous, voluntary reporting systems and the problems associated with estimating the total exposure to the drug. With these limitations in mind, the following data have been generated from post-marketing reports collected for lamotrigine. The adverse experiences included are those believed to be probably causally related to lamotrigine (at least in some instances) and are grouped by body system with an estimate of the frequency with which the reaction may be seen in the lamotrigine treated patient population (whether or not due to the drug in individual cases).

Psychiatric disorders

Mania

In New Zealand, of the 75 reports of adverse events with lamotrigine, three of them detailed a manic reaction. The WHO database received 99 reports of manic reactions associated with the use of lamotrigine, including six reports in patients of 18 years of age or below. Of the reports in patients under 18, indications were both for bipolar disorder and epilepsy.

Digestive disorders

Uncommon: gastrointestinal disturbances, e.g. nausea, vomiting, diarrhoea, anorexia

Haematological disorders

Uncommon: transient leucopenia or thrombocytopenia

Nervous system disorders

Uncommon: aggression, agitation, ataxia, confusion, dizziness, drowsiness, irritability, tremor, diplopia, blurred vision and conjunctivitis

Very rare: increase in seizure frequency

Dermatological disorders

Common: rash

Uncommon: erythema multiforme, Stevens-Johnson syndrome

Rare: exfoliative dermatitis, toxic epidermal necrolysis

Interactions

UDP-glucuronyl transferases have been identified as the enzymes responsible for the metabolism of lamotrigine. Cytochrome P450 is not involved in its elimination to any significant extent. Also, there is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. Hence, the likelihood that lamotrigine inhibits the elimination of drugs metabolised by cytochrome P450 is low. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Table 6 Effects of other drugs on glucuronidation of lamotrigine¹

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

¹ See **Dosage and Administration** for details

* Other oral contraceptive and hormone therapies have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters; see **General dosing recommendations - Women taking hormonal contraceptives** and **Warnings and Precautions - Hormonal contraceptives**.

Interactions involving anti-epileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain anti-epileptic drugs (such as phenytoin, carbamazepine, phenobarbitone and primidone) that induce hepatic drug-metabolising enzymes induce the metabolism glucuronidation of lamotrigine and enhance the metabolism of lamotrigine.

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

In a study in healthy adult volunteers using doses of 200 mg lamotrigine and 1,200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine.

In a study of healthy volunteers, co-administration 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. However, the incidence of adverse effects was higher during combination therapy (90%) than during lamotrigine and placebo (48%). Adverse effects were predominantly related to the central nervous system or gastrointestinal tract, including dizziness, headache and nausea.

Based on a retrospective analysis of plasma levels in patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. The results suggested 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 administration of pregabalin (200 mg three times daily) administration. There is no pharmacokinetic interaction between lamotrigine and pregabalin.

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

In a study of patients with epilepsy, co-administration 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. Increases in serum concentrations of zonisamide, leading to symptoms and signs of zonisamide toxicity, have been reported when lamotrigine was added to previously stable zonisamide therapy.

Although changes in the plasma concentrations of other anti-epileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant anti-epileptic

drugs. Evidence from *in vitro* studies suggested that lamotrigine does not displace other anti-epileptic 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 6 days to 20 healthy subjects was not altered by co-administration of 100 mg/day lamotrigine.

In a steady-state pharmacokinetic interaction study in healthy adult volunteers, daily dose of olanzapine 15 mg 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 daily did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single-dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone. In clinical trials of patients who took risperidone with lamotrigine or placebo, 4 out of 53 patients (7.5%) who received lamotrigine and risperidone reported the occurrence of somnolence or sedation, compared to 2 out of 62 patients (3.2%) who had taken placebo and risperidone.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine (100 mg) in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

In vitro inhibition experiments indicated that the formation of lamotrigine's primary metabolite, 2-N-glucuronide, was minimally affected by co-incubation with sodium valproate, amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol or lorazepam. The largest effect was observed with sodium valproate (which is known to reduce the clearance of lamotrigine *in vivo*) followed by bupropion. However, since bupropion had minimal effect on lamotrigine (see above), the risk of a clinically relevant interaction with amitriptyline, clonazepam, haloperidol or lorazepam is unlikely. The results also suggested that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline, trazodone or fluoxetine. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, ethinyloestradiol 30 mcg and levonorgestrel 150 mcg in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and C_{max} , respectively. Serum lamotrigine concentrations gradually increased during the course of

the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy (see **General dosing recommendations - Women taking hormonal contraceptives** and **Warnings and Precautions - Hormonal contraceptives**).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady-state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max} , respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. However, measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see Warnings and Precautions). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medications

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (see Dosage and Administration).

In a study in healthy volunteers, lopinavir or ritonavir approximately halved the plasma concentrations of lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir or ritonavir, the treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (see Dosage and Administration).

A study in healthy male volunteers found that there was a slightly enhanced elimination of lamotrigine in the presence of paracetamol but this was not considered to be clinically significant.

Overdosage

Symptoms

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

Pharmaceutical Precautions

Storage

Store below 25°C; protect from light and moisture

Shelf-life

36 months for all strengths of tablets

Medicines Classification

Prescription Medicine

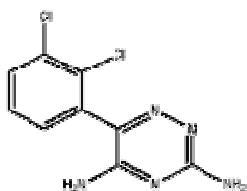
Package Quantities

Arrow - Lamotrigine 2 mg and 5 mg: Blister packs of 30 tablets

Arrow - Lamotrigine 2 mg, 5 mg, 25 mg, 50 mg, 100 mg and 200 mg:
Blister packs of 56 tablets

Further Information

Lamotrigine is a white to pale cream coloured powder, slightly soluble in ethanol and chloroform and very slightly soluble in water. The chemical name of lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Its structural formula is:



C₉H₇Cl₂N₅ Molecular weight: 256.09 CAS: 84057-84-1

Arrow - Lamotrigine Tablets contain the following excipients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, povidone, saccharin sodium, purified talc, magnesium stearate and blackcurrant flavour. The tablets are gluten free.

Name and Address

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