

# MOGINE

## Lamotrigine 25 mg, 50 mg, 100 mg and 200 mg Tablets

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### Name of the Drug

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MOGINE

Lamotrigine 25 mg, 50 mg, 100 mg and 200 mg tablets.

Severe, potentially life-threatening rashes have been reported in association with the use of lamotrigine, particularly in children. Accordingly, lamotrigine should be discontinued at the first sign of rash unless the rash is clearly not drug related. (See **Dosage and administration**).

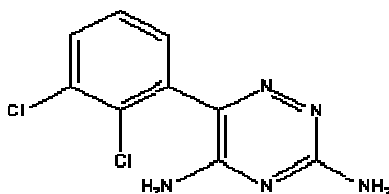
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### Description

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Lamotrigine is a substituted asymmetric triazine. It is a white to pale cream coloured powder. It is slightly soluble in ethanol and chloroform, and very slightly soluble in water. The pKa of lamotrigine at 25 °C is 5.7. The chemical name for lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. The CAS Number is 84057-84-1 and the molecular weight: 256.1.

The structural formula is:



MOGINE tablets contain as excipients: calcium carbonate, sorbitol, cellulose-microcrystalline, crospovidone, starch- maize, purified talc, saccharin sodium, sodium stearyl fumarate, colloidal anhydrous silica, blackcurrant flavour (ARTG No. 11133).

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### Pharmacology

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#### *Mechanism of Action*

Lamotrigine is an anticonvulsant and its action is uncertain. The results of neurochemical and electrophysiological studies with various *in vitro* and *in vivo* preparations indicate that lamotrigine can inhibit voltage gated sodium channels and reduce the release of glutamate, an excitatory amino acid implicated in the pathophysiology of epilepsy. It is possible that these effects underlie inhibition of the sustained repetitive firing of action potentials characteristic of neurones in epileptic foci, thereby limiting the spread of seizures.

In tests designed to evaluate the central nervous system effects of drugs, the results obtained using doses of 240 mg lamotrigine administered to healthy male and female volunteers did not differ from placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, increased body sway and produced subjective sedative effects.

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

## ***Pharmacokinetics***

### **Absorption**

In healthy volunteers, lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. The peak plasma concentration occurs approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected.

### **Distribution**

Lamotrigine is 55 % bound to plasma proteins; it is unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 L/kg. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary.

### **Metabolism**

Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers there is a modest induction of its own metabolism. The enzymes identified as those responsible for lamotrigine metabolism are UDP-glucuronyl transferases. Based on the data available, there is no clinical evidence that lamotrigine induces mono-oxygenase enzymes to an extent that would cause important interactions with drugs metabolised by these enzymes.

Mean steady state clearance in healthy adults is  $39 \pm 14$  mL/min. Ninety-four percent 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 man 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 (HPLC) radiodetection revealed the presence of another N-glucuronide metabolite present at about one-tenth of the concentration of the major metabolite.

### **Elimination**

Clearance and half-life are independent of dose. The mean elimination half-life is 24 to 35 hours and the pharmacokinetic profile is linear up to 450 mg, being the highest single dose tested. The half-life of lamotrigine is greatly affected by the use of concomitant medicines with a mean value of approximately 14 hours when given with enzyme inducing drugs such as carbamazepine and phenytoin, and increasing to a mean value of approximately 70 hours when co-administered with sodium valproate

alone (see **Dosage and administration**).

### ***Special Populations***

#### **Children (under 12 years)**

Clearance adjusted for bodyweight is higher in children aged 12 years of age and under when compared to adults, with the highest values in children under 5 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 given with enzyme inducing drugs such as carbamazepine and phenytoin, and increasing to mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone (see **Dosage and administration**).

#### **Elderly (65 to 76 years)**

Pharmacokinetic analyses were performed to yield the following results after studying a population including both young and elderly patients with epilepsy, enrolled in the same trials. The results 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 mL/min to 37 mL/min between the two groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly individuals 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 (0.31-0.65 mL/min/kg) obtained in 9 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 hemodialysis were each given a single 100 mg dose of lamotrigine. Mean CL/F were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between hemodialysis), and 1.57 mL/min/kg (during hemodialysis) compared to 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between hemodialysis) and 13.0 hours (during hemodialysis), 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 hemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's antiepileptic drug (AED) regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (see **Precautions**).

#### **Hepatic Impairment:**

A single-dose pharmacokinetic study was performed in 24 individuals with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31 mL/min, 0.24 mL/min 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. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see **Dosage and administration**).

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## Clinical Trials

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### ***Adult Add-on Treatment of Partial and Generalised Seizures***

The efficacy and safety of Lamotrigine has been demonstrated in 6 double blind, placebo controlled, crossover studies (n=221) with duration of Lamotrigine treatment ranging from 8 - 12 weeks, using doses up to 400 mg. Additionally, a double blind, placebo controlled, parallel study was performed of 2 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 with placebo significantly favoured lamotrigine in 5 of the 6 crossover trials. Overall 23 % (range 7 – 67 %) of patients in the controlled crossover trials showed a  $\geq 50$  % reduction in total seizures in lamotrigine compared with placebo. In the controlled parallel study, the median reduction (%) from baseline in total seizures during weeks 13 - 24 was 14 % on placebo compared with 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 effects were ataxia, dizziness, and diplopia and occurred more frequently with 500 mg lamotrigine than 300 mg lamotrigine in the controlled parallel study. Across the controlled trials, approximately 10 % of patients on lamotrigine developed a rash compared with 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 two weeks, followed by 50 mg daily for the next two weeks, to achieve a maintenance dose of 100 to 200 mg/day by weeks 5 - 6 (see **Interactions and Adverse effects**).

### ***Paediatric Add-on Therapy***

The safety and efficacy of lamotrigine has been demonstrated in 285 children with refractory epilepsy aged 2 to 12 years in 5 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  $\geq 50$  % reduction in seizures. The modal maintenance dose was 5 - 15 mg/kg for those not taking valproate and 1 - 5 mg/kg for those taking valproate. 7 % of patients discontinued lamotrigine with a rash. In patients on concomitant valproate, 2 % withdrew with a rash when their daily dose of Lamotrigine in the first week of treatment was  $\leq 0.5$  mg/kg compared with 13 % withdrawn with rash at an initial dose of Lamotrigine  $>0.5$  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 increase 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 3 antiepileptic drugs including carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, lorazepam, nitrazepam, oxcarbazepine, phenobarbitone, primidone, phenytoin, sodium valproate or vigabatrin. There are no data available on the use of lamotrigine as the sole drug treatment of Lennox-Gastaut Syndrome, as no single drug is likely to be of benefit.

After a 4 week run in period, patients (age range 2 - 28 years) were randomised to receive either Lamotrigine (n=79) (age range 3 - 25) 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 with 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. Four percent of add-on lamotrigine patients and 8 % of add-on placebo patients were withdrawn with adverse experiences. 3 % discontinued lamotrigine because of rash compared with 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. No patients on lamotrigine were withdrawn because of worsening seizures, however 4 % of patients on placebo were withdrawn.

### ***Clinical efficacy in the prevention of depressive episodes in patients with bipolar disorder***

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

Clinical study SCAB2003 was a multicentre, double-blind, double-dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using 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 multi-centre, 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 had recently 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 electroconvulsive therapy (ECT).

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In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on lamotrigine therapy was not significantly different to placebo.

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## **Indications**

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### ***Epilepsy***

#### **Adults (over 12 years of age)**

MOGINE 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)**

MOGINE 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-Gaustaut syndrome.

### ***Bipolar Disorder (Adults over 18 years)***

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

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### **Contraindications**

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Lamotrigine is contraindicated in individuals with known hypersensitivity to lamotrigine, or to any other ingredient in MOGINE tablets (**see Description**).

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### **Precautions**

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#### ***Skin Rash***

**SEE BOXED WARNING REGARDING THE RISK OF SEVERE, POTENTIALLY LIFE-THREATENING RASH ASSOCIATED WITH THE USE OF LAMOTRIGINE.**

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after commencing lamotrigine treatment. The majority of rashes are mild and self-limiting; however there have been cases where serious rashes requiring hospitalisation and discontinuation of lamotrigine have been reported. These have included potentially life-threatening rashes such as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (**See Adverse effects**).

Although benign rashes also occur with lamotrigine, it is not possible to predict reliably which rashes will prove to be life threatening. In adults enrolled in studies utilising 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 SJS (1 in 1000). In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000.

The risk of serious skin rashes is higher in children than in adults. A number of studies have been conducted and the available data suggests that the incidence of rashes associated with hospitalisation in children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash can be mistaken for an infection.

Doctors should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy.

Additionally the overall risk of rash appears to be strongly associated with:

- High initial doses of lamotrigine and exceeding the recommended dose, hence escalation of lamotrigine therapy (**see Dosage and administration**).
- Concomitant use of sodium valproate, which increases the mean half-life of lamotrigine nearly two fold (**see Dosage and administration**).

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

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure.

**It is important to note that early manifestations of hypersensitivity (eg. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and Mogenic should be discontinued if an alternative aetiology cannot be established.**

### ***Epilepsy***

Abrupt withdrawal of MOGINE, as with other antiepileptic drugs may lead to rebound seizures. Unless safety concerns (for example serious skin reactions) require an abrupt withdrawal, the dose of MOGINE should be gradually decreased over a period of two weeks.

When concomitant antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or other antiepileptic drugs are added-on to lamotrigine monotherapy, considerations should be taken into account of the effect this may have on lamotrigine pharmacokinetics (**See Interactions**).

### ***Bipolar Disorder***

#### **Children and adolescents (less than 18 years of age)**

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

#### **Clinical worsening and suicide risk associated with bipolar disorder**

Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

High risk 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, appear to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal

ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patients' presenting symptoms.

## ***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 one week of inactive medication (eg “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 (**see Dosage and administration**).

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

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

### **Effects of lamotrigine on hormonal contraceptive efficacy**

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinylloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (**see Interactions**). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with MOGINE 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; hence there is a possibility of interference with folate metabolism during long-term therapy. During prolonged human dosing, however, lamotrigine did not induce significant changes in the haemoglobin concentration; mean corpuscular volume, or serum or red blood cell folate concentrations up to a year, or red blood cell folate concentrations 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.

## ***Hepatic Impairment***

Lamotrigine is cleared primarily by metabolism in the liver. MOGINE should be administered with caution in patients with hepatic impairment as clearance is reduced (see **Dosage and administration**).

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multiorgan failure and disseminated intravascular coagulation, sometimes with a fatal outcome, this is evident in the reports found in the literature. Similar cases have occurred in association with the use of lamotrigine.

## ***Other Precautions***

### **Suicidality**

An analysis of reports of suicidality (suicidal behavior 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 behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine 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. The relative risk of suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class of psychiatric or other conditions.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

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

### **Patients taking other lamotrigine containing preparations:**

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

### **Mutagenicity**

Lamotrigine was not genotoxic in assays for gene mutation or chromosomal damage.

### **Carcinogenicity**

There was no evidence of carcinogenicity following daily oral administration of lamotrigine to mice and rats for up to two years at doses of up to 30 and 10 mg/kg respectively.

## **Fertility**

Fertility was reduced following oral administration of lamotrigine to male and female rats at a dose eliciting signs of toxicity (20 mg/kg/day). There is no experience of the effect of lamotrigine on human fertility.

## ***Effect on ability to drive or operate machinery***

Two studies have been conducted to demonstrate 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 effects of a neurological nature, such as dizziness and blurred vision, have been reported. As there is individual variation in response to all antiepileptic drug therapy, patients should consult their doctor on the specific issues of driving and epilepsy before commencing treatment.

## ***Use in Pregnancy (Category B3)***

It is recommended that women on antiepileptic drugs receive pre-pregnancy counselling with regard to the risk of foetal abnormalities. MOGINE should not be used in pregnancy unless, in the opinion of the doctor, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus. The risk to the mother and foetus of uncontrolled epilepsy should be considered when deciding on treatment options.

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 MOGINE therapy should be ensured.

Antiepileptic drugs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication.

There are insufficient data available on the use of lamotrigine in human pregnancy to evaluate its safety. Lamotrigine is a weak inhibitor of dihydrofolate reductase and studies in rats have shown a decrease in folic acid during pregnancy. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. Women who are planning to become pregnant, or who are pregnant, while being treated with MOGINE should take a folate supplement before conception and for the first 12 weeks of pregnancy, for example 5 mg of folate daily. Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered to pregnant women.

Reproductive toxicology studies with lamotrigine in mice, rats and rabbits at doses up to 100 mg/kg/day, 25 mg/kg/day and 30 mg/kg/day, respectively, did not reveal a clear teratogenic effect. An increased incidence of poorly ossified skeletal elements and rib anomalies, foetal weight decreases, prolonged gestation, fewer pups, increased incidence of still births, and reduced pup viability during lactation were observed in rats following administration of up to 25 mg/kg/day. These foetotoxic effects may have been due to maternal toxicity.

### ***Use in Lactation***

There is limited information on the use of lamotrigine in lactation. Preliminary data indicate that lamotrigine passes into breast milk in concentrations usually of the order of 40-60 % of the plasma concentration. In a small number of infants known to have been breastfed, the plasma concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant.

Lamotrigine and/or its metabolites pass into the milk of lactating rats (approximately 5 % of the dose was transferred to the litter). Oral administration of lamotrigine 20 mg/kg/day to rats during late gestation and lactation was associated with reduced pup viability, concomitant with signs of maternal toxicity.

### ***Interactions***

There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

#### **Table of effects of other drugs on glucuronidation of lamotrigine (see Dosage and Administration):**

<b>Drugs that significantly inhibit glucuronidation of lamotrigine</b>	<b>Drugs that significantly induce glucuronidation of lamotrigine</b>	<b>Drugs that do not significantly inhibit or induce glucuronidation of lamotrigine</b>
<ul style="list-style-type: none"><li>▪ Valproate</li></ul>	<ul style="list-style-type: none"><li>▪ Carbamazepine</li><li>▪ Phenytoin</li><li>▪ Primidone</li><li>▪ Phenobarbitone</li><li>▪ Rifampicin</li><li>▪ Lopinavir/ritonavir</li><li>▪ Ethinylloestradiol/levonorgestrel combination*</li></ul>	<ul style="list-style-type: none"><li>▪ Lithium</li><li>▪ Bupropion</li><li>▪ Olanzapine</li><li>▪ Oxcarbazepine</li><li>▪ Felbamate</li><li>▪ Gabapentin</li><li>▪ Levetiracetam</li><li>▪ Pregabalin</li><li>▪ Topiramate</li><li>▪ Zonisamide</li></ul>

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

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

#### **Effect of hormonal contraceptives on lamotrigine pharmacokinetics**

In a study of 16 female volunteers, 30 mcg ethinylloestradiol/150 mcg levonorgestrel

in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52 % and 39 % reduction in lamotrigine AUC and  $C_{max}$ , respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (eg “pill-free week”), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

#### **Effect of lamotrigine on hormonal contraceptive pharmacokinetics**

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the 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, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH on ovarian ovulatory activity is unknown (**see 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 MOGINE and concurrent hepatic enzyme inducers should be used (**see Dosage and administration**).

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

Antiepileptic drugs (such as phenytoin, carbamazepine, phenobarbitone and primidone), which induce hepatic drug-metabolising enzymes, enhance the metabolism of lamotrigine (**see Dosage and administration**). Other drug-classes, which induce hepatic drug-metabolising enzymes, may also enhance the metabolism of lamotrigine.

Sodium valproate, which competes with lamotrigine for hepatic drug metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold (**See Precautions and Dosage and administration**).

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

Approximately 96 % of a given dose of lamotrigine is eliminated by conjugation

metabolism mediated by glucuronyl-transferases. Cytochrome P450 is not involved in the elimination of lamotrigine to any significant extent. Therefore the likelihood that lamotrigine inhibits the elimination of drugs metabolised by cytochrome P450 is low.

The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine.

*In vitro* experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was inhibited by co-incubation with sodium valproate, bupropion, clonazepam, amitriptyline, haloperidol, and lorazepam. Sodium valproate is known to reduce the clearance of lamotrigine in vivo (see above). In these experiments, the largest effect (after that of sodium valproate) was observed with bupropion; however, multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of a low dose (100 mg) of lamotrigine in 12 subjects and caused only a slight increase in the AUC of lamotrigine glucuronide.

This observation suggests that the risk of a clinically relevant interaction with amitriptyline, clonazepam, haloperidol or lorazepam is therefore unlikely. The in vitro experiments 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 microsomes suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

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## Adverse effects

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In a double blind, add-on placebo controlled clinical trials, skin rashes occurred in 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 in all clinical trials. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine.

Serious, potentially life threatening skin rashes, including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell Syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (**See Precautions**).

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

- High initial doses of lamotrigine and exceeding the recommended dose, hence escalation of MOGINE therapy (**see Dosage and administration**)
- Concomitant use of sodium valproate, which increases the mean half-life of lamotrigine nearly two fold (**see Dosage and administration**).

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 *below*). The syndrome shows a wide spectrum of clinical severity and may rarely lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (eg. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should

be evaluated immediately and lamotrigine should be discontinued if an alternative aetiology cannot be established.

The table below (Table 1) presents a comparison of adverse experiences reported during clinical trials with lamotrigine. Data are presented, in decreasing order of the incidence seen in lamotrigine patients, from the pooled placebo controlled add-on studies that have been conducted with lamotrigine. For comparison, data are also presented from pooled monotherapy studies that have been conducted with lamotrigine. These adverse experiences have been reported most commonly during the initial weeks of treatment with lamotrigine.

Adverse Experience	% Reporting from Pooled Add-on Studies <sup>1</sup>		% Reporting from Pooled Monotherapy Studies <sup>2</sup>		
	Lamotrigine (n = 242)	Placebo (n = 233)	Lamotrigine (n = 443)	Carbamazepine (n = 246)	Phenytoin (n = 95)
Diplopia	21	8	<1	3	2
Dizziness	19	12	8	14	12
Ataxia	19	5	<1	6	12
Headache	17	14	20	17	19
Asthenia	16	18	16	24	29
Nausea	16	7	10	10	4
Somnolence	10	9	8	20	28
Vomiting	9	3	4	4	1
Respiratory Disorder	7	7	<1	1	1
Rash	6	5	12	14	9
Pain	6	4	2	2	5
Pharyngitis	3	<1	5	4	2
Flu syndrome	<1	<1	5	4	3
Insomnia	4	<1	6	2	3
Menstrual disorder	1	<1	1	5	-
Tremor	3	2	2	<1	8
Lung disorder	<1	<1	1	2	6
Depression	4	3	2	5	3
Amnesia	3	4	3	3	5
Thinking abnormality	2	2	2	4	5

<sup>1</sup> Adverse experiences with incidence  $\geq 5\%$  of Lamotrigine patients (includes corresponding rates for monotherapy events).  
<sup>2</sup> Adverse experiences with incidence  $\geq 5\%$  in any treatment group (includes corresponding rates for add-on events).  
- Not reported

Agitation, confusion, drowsiness, hallucinations, irritability/aggression, tiredness, has also been reported. In children hyperkinesia has been reported (5 %). Very rarely, lupus-like reactions have been reported. Arthralgia was reported commonly during the clinical development program for lamotrigine in bipolar disorder.

There have been reports of haematological abnormalities, which may or may not be associated with the hypersensitivity syndrome. These have included anaemia, leucopenia, neutropenia, pancytopenia, thrombocytopenia and very rarely agranulocytosis and aplastic anaemia.

Movement disorders such as ataxia, nystagmus, tics, tremor and unsteadiness have also been reported. 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.

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.

The incidence of adverse reactions to marketed drugs, such as MOGINE, 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 table below has been generated from post-marketing data 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).

#### **FREQUENCY ESTIMATES OF ADVERSE REACTIONS SEEN WITH LAMOTRIGINE FROM POST-MARKETING DATA**

##### *Digestive Disorders: †*

Uncommon: Gastro-intestinal disturbances, eg anorexia, diarrhoea, nausea, vomiting

##### *Haematological Disorders: †*

Uncommon: Transient leucopenia or thrombocytopenia

##### *Nervous System Disorders: †*

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

Very rare: Increase in seizure frequency, mania

##### *Dermatological Disorders: †*

Common: Rash

Uncommon: Erythema multiforme, Stevens Johnson Syndrome

Rare: Exfoliative dermatitis, toxic epidermal necrolysis

<sup>†</sup> *Frequency estimates:*

Common: more than one per hundred patients.

Uncommon: between one per thousand and one per hundred patients.

Rare: less than one per thousand patients.

Very Rare: fewer than one per ten thousand patients.

- suicidal behaviour
- suicidal ideation
- emergence or worsening of existing depression

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## **Dosage and administration**

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### ***Epilepsy***

**Since the minimum strength available for MOGINE is the 25 mg tablet, other lamotrigine products with 2 mg and 5 mg strengths should be used instead of MOGINE if the calculated dose is less than 25 mg.**

It is strongly recommended that therapy with MOGINE be initiated at the recommended doses. Careful incremental titration of the dose may decrease the severity of skin rashes.

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

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

If a calculated dose of MOGINE (eg for use in children (epilepsy only) or patients with hepatic impairment) cannot be divided into multiple lower strength tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

### **Restarting Therapy**

Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued lamotrigine for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see **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 MOGINE not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

## ***Epilepsy***

### **Dosage in EPILEPSY add-on therapy**

#### **Adults (over 12 years of age)**

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

In those patients taking enzyme inducing AEDs or other medications (see Interactions) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial MOGINE dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks.

Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200- 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 MOGINE dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses.

#### **Recommended dose escalation in Epilepsy for adults (over 12 years of age) on combined drug therapy:**

		<b>Weeks 1 + 2</b>	<b>Weeks 3 + 4</b>	<b>Maintenance Dose</b>
	Add-on therapy with Valproate regardless of any concomitant medications	12.5 mg (given 25mg alternate days)	25mg (once a day)	100-200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25-50 mg every 1-2 weeks
Add-on therapy without Valproate	This dosage regimen should be used with inducers of lamotrigine glucuronidation e.g. phenytoin, carbamazepine, phenobarbitone and primidone (see Interactions)	50 mg (once a day)	100mg (two divided doses)	200-400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1-2 weeks

		<b>Weeks 1 + 2</b>	<b>Weeks 3 + 4</b>	<b>Maintenance Dose</b>
	This dosage should be taken with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions).	25 mg (once a day)	50 mg (once a day)	100 - 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 - 100 mg every one to two weeks
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen as recommended for MOGINE with concurrent valproate should be used.				

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

### **Children (2 to 12 years of age)**

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

In those patients taking enzyme inducing AEDs or other medications (see Interactions) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial MOGINE dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in 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 MOGINE dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

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

**Recommended dose escalation in Epilepsy for children aged 2-12 years (total daily dose in mg/kg bodyweight/day) on combined drug therapy:**

		<b>Weeks 1 + 2</b>	<b>Weeks 3 + 4</b>	<b>Maintenance Dose</b>
Note: If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.				
Add-on therapy with Valproate regardless of any other concomitant medication		0.15 mg/kg (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses) to a maximum of 200mg/day
Add-on therapy without Valproate	This dosage regimen should be used with inducers of lamotrigine glucuronidation e.g. phenytoin, carbamazepine, phenobarbitone and primidone (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 (two divided doses) to a maximum of 400 mg/day
	This dosage should be taken with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions).	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 - 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen as recommended for MOGINE with concurrent valproate should be used.				

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

It is likely that patients aged 2-6 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.

**General Dosing Recommendations for Epilepsy**

When other antiepileptic drugs (AEDs) are added-on to treatment regimes containing MOGINE, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (**see Interactions**).

## ***Bipolar Disorder***

### **Adults (18 years of age and over)**

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

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

The following transition regimen should be followed to prevent recurrence of depressive episodes. The transition regimen involves escalating the dose of MOGINE to a maintenance stabilisation dose over six weeks after which other psychotropic 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.

### **Recommended dose escalation to the maintenance total daily stabilisation dose for adults (over 18 years of age) treated for Bipolar Disorder**

<b>Treatment Regimen</b>	<b>Weeks 1-2</b>	<b>Weeks 3-4</b>	<b>Week 5</b>	<b>Target Stabilisation Dose (Week 6)**</b>
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for MOGINE with concurrent valproate, should be used.				
<b>a) Adjunct therapy with Enzyme inhibitors e.g. Valproate</b>	12.5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
<b>b) Adjunct therapy with Enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking Valproate (see Interactions)</b>	50 mg (once a day)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
<b>c) Adjunct therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)</b> <b>OR</b> <b>Monotherapy with lamotrigine</b>	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200 mg (Range 100-400 mg) (once a day or two divided doses)

\*\*The Target stabilisation dose will alter depending on clinical response.

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

**b) Adjunct therapy with Enzyme inducers (e.g. carbamazepine and phenobarbitone in patients NOT taking Valproate) (see Interactions):** In those patients taking enzyme inducing drugs such as carbamazepine or phenobarbitone and NOT taking valproate, the initial MOGINE dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. The dose should be increased to 200 mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day however, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses which may be given from week 7.

**c) Adjunct therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see Interactions):** The initial MOGINE dose in patients taking concomitant drugs with no known/theoretical pharmacokinetic interaction with lamotrigine is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100-400 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.

**Maintenance stabilisation total daily dose in Bipolar Disorder following withdrawal of concomitant psychotropic or anti-epileptic drugs**

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

Treatment Regimen	Week 1	Week 2	Week 3 onwards*
lamotrigine glucuronidation (see Interactions).	(Range 100-400 mg)		

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

**(a) Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate:** The dose of MOGINE 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 enzyme inducers e.g. carbamazepine, depending on original maintenance dose (see Interactions):** The dose of MOGINE should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

**(c) Following withdrawal of adjunct therapy with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions):** The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

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

**Adjustment of MOGINE daily dosing in patients with Bipolar Disorder following the addition of other medications**

Treatment Regimen	Current lamotrigine Stabilisation dose (mg/day)	Week 1	Week 2	Week 3 onwards
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for MOGINE with concurrent valproate, should be used.				
<b>(a) Addition of enzyme inhibitors e.g. valproate, depending on original dose of Mogine</b>	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>(b) Addition of enzyme inducers e.g. carbamazepine in patients NOT taking valproate and depending on original dose of Mogine (see Interactions)</b>	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
<b>(c) Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation</b>	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			

Treatment Regimen	Current lamotrigine Stabilisation dose (mg/day)	Week 1	Week 2	Week 3 onwards
(see Interactions).				

### **Discontinuation of MOGINE 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 MOGINE without a step-wise reduction of dose.

### **Children and Adolescents (less than 18 years of age)**

MOGINE is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (**see 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 for special patient populations***

### **Women taking hormonal contraceptives**

#### **(a) Starting MOGINE in patients already taking hormonal contraceptives:**

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (**see Precautions and Interactions**), no adjustments to the recommended dose escalation guidelines for MOGINE should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether MOGINE is added to an inhibitor of lamotrigine glucuronidation e.g. valproate; whether MOGINE is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampin; or whether MOGINE is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (see Table 1 for epilepsy and Table 3 for bipolar patients).

#### **(b) Starting hormonal contraceptives in patients already taking maintenance doses of MOGINE and NOT taking inducers of lamotrigine glucuronidation:**

The maintenance dose of Mogine may need to be increased by as much as two-fold according to the individual clinical response (**see Precautions and Interactions**).

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

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

### **Elderly (over 65 years of age)**

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

### **Hepatic impairment**

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

### **Renal impairment**

Caution should be exercised when administering MOGINE to patients with renal failure. For patients with end-stage renal failure, initial doses of MOGINE should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (**see Precautions and Pharmacokinetic Properties**).

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## **Overdosage**

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### *Symptoms*

Symptoms and signs of overdose have resulted in the following clinical features: ataxia, blurred vision, coma, dizziness, headache, impaired consciousness, increased seizures, nystagmus, somnolence and vomiting. Acute ingestion of doses in excess of 10 to 30 times the maximum therapeutic dose has been reported. Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal.

A patient who ingested a dose calculated to be between 4 and 5 g lamotrigine was admitted to hospital with coma lasting 8 - 12 hours, followed by recovery over the next 2 - 3 days. A further patient who ingested 5.6 g lamotrigine was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours.

### *Management*

No specific antidotes are available to treat overdosage. In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Measures should be taken to protect the airways, as consciousness may be impaired.

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## **Presentation**

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**MOGINE 25 mg tablets:** White to off-white, modified square shape, engraved with “L” and “25” on one side, plain on the other side.

**MOGINE 50 mg tablets:** White to off-white, modified square shape, engraved with “L” and “50” on one side, plain on the other side.

**MOGINE 100 mg tablets:** White to off-white, modified square shape, engraved with “L” and “100” on one side, plain on the other side.

**MOGINE 200 mg tablets:** White to off-white, modified square shape, engraved with “L” and “200” on one side, plain on the other side.

***Storage:***

MOGINE tablets should be stored below 25 °C and should be kept in a place where they will remain dry and away from light. The shelf-life is 3 years.

***Pack quantities***

MOGINE Tablets are available in packs of 56 tablets.

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**Medicine Classification**

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Prescription Medicine

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**Name and Address of Sponsor**

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**Date of Preparation**

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