

Lamotrigine

Core Safety Profile

4.2 Posology and method of administration

Epilepsy

Children below 2 years

There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus <product name> is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2.

General dosing recommendations for <product name> in special patient populations

Women taking hormonal contraceptives

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation

The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous

hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation

The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

Starting lamotrigine in patients already taking hormonal contraceptives

Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation

Adjustment to the recommended maintenance dose of lamotrigine may not be required.

Use with atazanavir/ritonavir

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Use with lopinavir/ritonavir

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if

lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening rashes such as Stevens–Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

The risk of serious skin rashes in children is higher than in adults. Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in epileptic children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash can be mistaken for an infection, physicians should consider the possibility of a reaction to lamotrigine treatment in children that develop symptoms of rash and fever during the first eight weeks of therapy.

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

- high initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

Caution is also required when treating patients with a history of allergy or rash to other AEDs as the frequency of non-serious rash after treatment with lamotrigine was approximately three times higher in these patients than in those without such history.

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

Rash 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 section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and <product name> discontinued if an alternative aetiology cannot be established.

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including <product name> . Therefore patients receiving <product name> for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinylloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

The interaction between other oral contraceptive or HRT treatments and lamotrigine 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 section 4.5). 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 has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). 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.

Patients taking other preparations containing lamotrigine

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

25, 50, 100 and 200 mg tablets:

Excipient of <product name> tablets

<product name> tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Development in children

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

Precautions relating to epilepsy

As with other AEDs, abrupt withdrawal of <product name> may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of <product name> should be gradually decreased over a period of two weeks.

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

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

Myoclonic seizures may be worsened by lamotrigine.

There is a suggestion in the data that responses in combination with enzyme inducers is less than in combination with non-enzyme inducing antiepileptic agents. The reason is unclear.

In children taking lamotrigine for the treatment of typical absence seizures, efficacy may not be maintained in all patients.

Precautions relating to bipolar disorder

Children and adolescents below 18 years

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.

4.5 Interactions with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Table 6: Effects of other medicinal products on glucuronidation of lamotrigine

Medicinal products that significantly inhibit glucuronidation of lamotrigine	Medicinal products that significantly induce glucuronidation of lamotrigine	Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine
Valproate	Phenytoin	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbitone	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate
	Ethinylestradiol/ levonorgestrel combination**	Zonisamide
	Atazanavir/ritonavir*	Lithium
		Bupropion
		Olanzapine

*For dosing guidance (see section 4.2)

** Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see sections 4.2 and 4.4).

Interactions involving antiepileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

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

There are reports in the literature of decreased lamotrigine levels when lamotrigine was given in combination with oxcarbazepine. However, in a prospective study in healthy adult volunteers using doses of 200 mg lamotrigine and 1200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine. Therefore in patients receiving concomitant therapy with oxcarbazepine, the treatment regimen for lamotrigine adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation should be used (see section 4.2).

In a study of healthy volunteers, coadministration of felbamate (1200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

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

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

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

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

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

Although changes in the plasma concentrations of other AEDs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant AEDs. Evidence from *in vitro* studies indicates that lamotrigine does not displace other AEDs from protein binding sites.

Interactions involving other psychoactive agents

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

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

In a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C_{max} of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

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

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, dosing with 30 µg ethinyloestradiol/150 µg 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 increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). 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 medicinal products

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 appropriate treatment regimen should be used (see section 4.2).

In a study in healthy volunteers, lopinavir/ritonavir approximately halved the plasma concentrations of lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and C_{max} of lamotrigine

(single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

4.6 Fertility, pregnancy and lactation

Risk related to antiepileptic drugs in general

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

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

Risk related to lamotrigine

Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although data are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).

If therapy with <product name> is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels (see section 4.4). Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels during pregnancy with a potential risk of loss of seizure control. After birth lamotrigine levels may increase rapidly with a risk of dose-related adverse events. Therefore lamotrigine serum concentrations should be

monitored before, during and after pregnancy, as well as shortly after birth. If necessary, the dose should be adapted to maintain the lamotrigine serum concentration at the same level as before pregnancy, or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Lactation

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

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

Fertility

Animal experiments did not reveal impairment of fertility by lamotrigine (see section 5.3).

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all AED therapy, patients taking <product name> to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.

No studies on the effects on the ability to drive and use machines have been performed. 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 reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how <product name> therapy affects them before driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

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

The following convention has been utilised for the classification of undesirable effects: - Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Epilepsy

Blood and lymphatic system disorders

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

Frequency not known: lymphadenopathy.

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

Immune system disorders

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

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and <product name> discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common: aggression, irritability.

Very rare: confusion, hallucinations, tics.

Nervous system disorders

During monotherapy clinical trials:

Very common: headache.

Common: somnolence, dizziness, tremor, insomnia.

Uncommon: ataxia.

Rare: nystagmus.

During other clinical experience:

Very common: somnolence, ataxia, dizziness, headache.

Common: nystagmus, tremor, insomnia.

Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.
Frequency not known: aseptic meningitis.

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

During monotherapy clinical trials:

Uncommon: diplopia, blurred vision.

During other clinical experience:

Very common: diplopia, blurred vision.

Rare: conjunctivitis.

Gastrointestinal disorders

During monotherapy clinical trials:

Common: nausea, vomiting, diarrhoea.

During other clinical experience:

Very common: nausea, vomiting.

Common: diarrhoea.

Hepato-biliary disorders

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

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

Skin and subcutaneous tissue disorders

Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

In double-blind, adjunctive clinical trials in adults, 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 eight weeks of starting treatment and resolves on withdrawal of <product name> (see section 4.4).

Serious potentially life-threatening skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) have been reported. Although the majority recover on withdrawal of lamotrigine

treatment, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

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 section 4.2)
- concomitant use of valproate (see section 4.2).

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

Musculoskeletal and connective tissue disorders

Very rare: lupus-like reactions.

General disorders and administration site conditions

Common: tiredness.

Bipolar Disorder

The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

Nervous system disorders

During bipolar disorder clinical trials:

Very common: headache.

Common: agitation, somnolence, dizziness.

Gastrointestinal disorders

During bipolar disorder clinical trials:

Common: dry mouth

Skin and subcutaneous tissue disorders

During bipolar disorder clinical trials:

Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Musculoskeletal and connective tissue disorders

During bipolar disorder clinical trials:

Common: arthralgia.

General disorders and administration site conditions

During bipolar disorder clinical trials:

Common: pain, back pain.

4.9 Overdose

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.

Treatment

In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).