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INSTRUCTION
for medical use

LANISTOR®

Composition:
active substance: lamotrigine;
1 tablet contains 25 mg, 50 mg, 100 mg lamotrigine;
excipients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), povidone, magnesium stearate.

Pharmaceutical form. Tablets.
Basic physico-chemical properties: white to off-white, round, flat, bevelled-edge, uncoated tablets debossed with "L" on one side and plain on other side.

Pharmacotherapeutic group. Other antiepileptics. Lamotrigine.
ATC code N03A X09.

Pharmacological properties.
Pharmacodynamics.
Lamotrigine is an antiepileptic drug whose mechanism of action is associated with blocking the potential-dependent sodium channels of presynaptic membranes of neurons in the phase of slow inactivation and inhibition of excess glutamate release (amino acids that play a significant role in the development of an epileptic attack).
Pharmacokinetics.
After oral administration it is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentration (C_{max}) occur approximately in 2.5 hours.
Lamotrigine is actively metabolized, the main metabolite is N-glucuronide. The average half-life in adults is 29 hours. Lamotrigine has a linear pharmacological profile. It is excreted mainly in the form of metabolites and partly unchanged, mainly with urine. The half-life in children is less than in adults.
Special patient populations
Children
Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing medicinal products such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone.
Elderly patients
Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to

a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39 mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) obtained in nine studies with non-elderly adults after single doses of 30 to 450 mg.

Patients with renal impairment

Twelve volunteers with chronic renal failure, and another six individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances 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 with 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 with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour hemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant antiepileptic drugs; reduced maintenance doses may be effective for patients with significant renal functional impairment.

Patients with hepatic impairment

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

Clinical characteristics.

Indications.

Epilepsy

Adults and adolescents aged 13 years and above

Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

Seizures associated with Lennox-Gastaut syndrome. Lamotrigine is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

Children and adolescents aged 2 to 12 years

Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Monotherapy of typical absence seizures.

Bipolar disorder

Adults (aged 18 years and above)

Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes.

Lamotrigine is not indicated for the acute treatment of manic or depressive episodes.

Contraindications.

Lanistor is contraindicated to patients with known hypersensitivity to lamotrigine or to any other component of the drug.

Interaction with other medicinal products and other forms of interaction.

Interaction studies have only been performed in adults.

Uridine 5'-diphospho (UDP) glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine.
There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.
Those drugs that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in table 1. Specific dosing guidance for these drugs is provided in "Dosage and administration" section. In addition, table 1 lists those drugs which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such drugs would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Table 1

Effects of medicinal products on the concentration of lamotrigine

Medicinal products that increase the concentration of lamotrigine	Medicinal products that decrease the concentration of lamotrigine	Medicinal products that have little or no effect on the concentration of lamotrigine
Valproate	Atazanavir/ritonavir*, carbamazepine ethinyloestradiol/levonorgestrel combination*, lopinavir/ritonavir, phenobarbitone, phenytoin, primidone, rifampicin	Aripiprazole, buproprion, felbamate, gabapentin, lacosamide, levetiracetam, lithium, olanzapine, oxcarbazepine, paracetamol, perampanel, pregabalin, topiramate, zonisamide

* For detailed information on dosage see "General dosing recommendations for lamotrigine in special patient populations" subsection of "Dosage and administration" section. For women taking hormonal contraceptives also see "Hormonal contraceptives" subsection in "Special warnings and precautions for use" section.

Interactions involving antiepileptic drugs (see "Dosage and administration" section).
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 "Dosage and administration" section).
Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, pheonbarbitone or primidone, the appropriate treatment regimen should be used (see "Dosage and administration" section).
There have been reports of central nervous system (CNS) 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 "Dosage and administration" section).
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 and levetiracetam do not influence the pharmacokinetics of each other.
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) during 35 days for epilepsy had no significant effect on the pharmacokinetics of lamotrigine.
Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200 mg/day, 400 mg/day, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.
In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10%.
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 level of lamotrigine glucuronide.
In a study in healthy adult volunteers, 15 mg olanzapine reduced the area under the concentration-time curve (AUC) and C_{max} of lamotrigine by an average of 24% and 20%, respectively. 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 a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (≥100 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30

mg/day over a 7-day period and continued once daily for a further 7 days. An average reduction of approximately 10% in AUC and C_{max} of lamotrigine was observed.
In vitro experiments indicated that the formation of lamotrigine's primary metabolite, the N-glucuronide, was minimally inhibited by amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol or lorazepam. 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. *In vitro* experiments also suggested that metabolism of lamotrigine was unlikely to be inhibited by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone.
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 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 "Special warnings and precautions for use" section). There is no need to adjust the recommended doses of lamotrigine solely through the use of hormonal contraceptives, but the maintenance dose of lamotrigine may be increased or decreased in most cases when starting or stopping hormonal contraceptives (see "Dosage and administration" section).
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 clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum follicle-stimulating hormone, luteinizing hormone 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 follicle-stimulating and luteinizing hormones, on ovarian ovulatory activity is unknown (see "Special warnings and precautions for use" section). The effects of doses of lamotrigine other than 300 mg/day have not been studied. Studies of other hormonal contraceptives 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 with lamotrigine and respective glucuronidation inducers should be used (see "Dosage and administration" section).
In a study in healthy volunteers, lopinavir/ritonavir approximately halved the plasma concentrations of lamotrigine by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the appropriate treatment regimen with lamotrigine and respective glucuronidation inducers should be used (see "Dosage and administration" section).
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 (see "Dosage and administration" section).
In a study in healthy adult volunteers, paracetamol 1 g (four times daily) reduced the plasma AUC and minimum concentration (C_{min}) of lamotrigine by an average of 20% and 25%, respectively.
Data from *in vitro* assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of Organic Transporter 2 (OCT 2) at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC_{50}

value of 53.8 µM. Co-administration of lamotrigine with renally excreted medicinal products, which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicinal products.
The clinical significance of this has not been clearly defined, however care should be taken in patients co-administered with these medicinal products.

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 (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (see "Adverse reactions" section).
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 lamotrigine studies suggest 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, 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, and concomitant use of valproate (see "Dosage and administration" section).
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.
HLA B*1502 allele in individuals of Asian (primarily Han Chinese and Thai) origin has been shown to be associated with the risk of developing SJS/TEN when treated with lamotrigine. If these patients are known to be positive for HLA B*1502, use of lamotrigine should be carefully considered.
All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.
If the patient has developed SJS, TEN or DRESS with the use of lamotrigine, treatment with lamotrigine must not be re-started in this patient at any time.
Rash has also been reported as part of DRESS; also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver, kidney and aseptic meningitis (see "Adverse reactions" section). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately, and lamotrigine discontinued if an alternative aetiology cannot be established. Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return

of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.
There have also been reports of photosensitivity reactions associated with lamotrigine use (see "Adverse reactions" section). In several cases, the reaction occurred with a high dose (400 mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

Haemophagocytic lymphohistiocytosis (HLH)

HLH has been reported in patients taking lamotrigine (see "Adverse reactions" section). HLH is characterised by signs and symptoms, like fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. HLH can be life threatening.
Patients should be informed of the symptoms associated with HLH and should be advised to seek medical attention immediately if they experience these symptoms while on lamotrigine therapy.
Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be promptly discontinued unless an alternative aetiology can 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 lamotrigine. Therefore, patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see "Interaction with other medicinal products and other forms of interaction" section). 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 "Dosage and administration" section).
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 hormone replacement therapy agents 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 (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum follicle-stimulating and luteinizing hormones (see "Interaction with other medicinal products and other forms of interaction" section). 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 "Pregnancy and lactation" section). 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
Lanistor should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.
Brugada-type ECG abnormalities
Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern have been reported in patients treated with lamotrigine.
Based on *in vitro* findings, lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia at therapeutically relevant concentrations in patients with heart disease. Lamotrigine behaves like a weak class Ib antiarrhythmic agent with associated potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risks. At therapeutic doses up to 400 mg/day, lamotrigine did not slow ventricular conduction (widen QRS) or cause QT prolongation in healthy individuals in a thorough QT study. The use of lamotrigine should be carefully considered in patients with clinically important structural or functional heart disease such as Brugada syndrome or other cardiac channelopathies, heart failure, ischemic heart disease, heart block or ventricular arrhythmias. If lamotrigine is clinically justified in these patients, consultation with a cardiologist before initiating lamotrigine should be considered.
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 lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of lamotrigine 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.
Excipients
The drug contains lactose. If the patient has an intolerance to some sugars, doctor's consultation is necessary before using this preparation.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

Pregnancy and lactation.
Risk related to antiepileptic drugs in general.
Specialist advice should be given to women who are of childbearing potential. Antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic drug therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.
Monotherapy should be used whenever possible because therapy with multiple antiepileptic drugs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.
Risk related to lamotrigine
Pregnancy
A large amount of epidemiological study data from more than 12,700 pregnancies exposed to lamotrigine monotherapy, including more than 9,100 pregnancies exposed during the first trimester, do not indicate that lamotrigine therapy at maintenance doses is associated with an increased risk of major congenital malformations.
Studies investigating the effect of doses higher than the usual maintenance dose of 100–200 mg per day on the risk of major congenital malformations have shown conflicting results. Some studies did not find evidence of a dose-response effect, however data from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) showed a statistically significant increase in the rate of major congenital malformations with dose of lamotrigine ≥325 mg per day, compared with doses <325 mg per day (OR 1.68, 95% CI 1.01–2.80). Therefore, if therapy with lamotrigine is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase. Since folic acid has a protective effect on the risk of neural tube defects folic acid supplementation when planning pregnancy and during early pregnancy is recommended.
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.
Animal studies have shown developmental toxicity.
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 mothers'. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.
The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant.
It is necessary to compare the potential benefits of breastfeeding with the potential risk of adverse reactions in the infant. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects, such as sedation, rash and poor weight gain.
Fertility
Animal experiments did not reveal impairment of fertility by lamotrigine.

Effects on ability to drive and use machines.
As there is individual variation in response to any AED therapy, patients taking lamotrigine to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.
No studies on the effects on the ability to drive and use machines have been performed. 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 lamotrigine therapy affects them before driving or operating machinery.

Dosage and administration.
Lanistor tablets should be swallowed whole, and should not be chewed or crushed.
If the calculated dose of lamotrigine (e.g. for treatment of children with epilepsy or patients with hepatic impairment) does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.
If the calculated dose of lamotrigine is less than 25 mg, lamotrigine preparations with the possibility of such a dosage should be used.
Restarting therapy
Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued it for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see "Special warnings and precautions for use" section). 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" section), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule.

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

Epilepsy

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (see table 2) and for children and adolescents aged 2 to 12 years (see table 3) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see "Special warnings and precautions for use" section).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see "Interaction with other medicinal products and other forms of interaction" section).

Table 2

Adults and adolescents aged 13 years and above – recommended treatment regimen in epilepsy

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy	25 mg/day (once a day)	50 mg/day (once a day)	100–200 mg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 50–100 mg every one to two weeks until optimal response is achieved. 500 mg/day has been required by some patients to achieve desired response.
Adjunctive therapy with valproate (inhibitor of lamotrigine glucuronidation – see "Interaction with other medicinal products and other forms of interaction" section).			
This dosage regimen should be used with valproate regardless of any concomitant medicinal products.	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	100–200 mg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 25–50 mg every one to two weeks until optimal response is achieved.
Adjunctive therapy without valproate and with inducers of lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).			
This dosage regimen should be used without valproate but with phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.	50 mg/day (once a day)	100 mg/day (two divided doses)	200–400 mg/day (two divided doses). To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved. 700 mg/day has been required by some patients to achieve desired response.
Adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).			

This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	25 mg/day (once a day)	50 mg/day (once a day)	100–200 mg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 50–100 mg every one to two weeks until optimal response is achieved.
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see «Interaction with other medicinal products and other forms of interaction" section), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

Table 3

Children and adolescents aged 2 to 12 years – recommended treatment regimen in epilepsy (total daily dose in mg/kg body weight/day) *

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy of typical absence seizures	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1–15 mg/kg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day* every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.
Adjunctive therapy with valproate (inhibitor of lamotrigine glucuronidation – see "Interaction with other medicinal products and other forms of interaction" section).			
This dosage regimen should be used with valproate regardless of any other concomitant medicinal products.	0.15 mg/kg/day (once a day)	0.3 mg/kg/day (once a day)	1–5 mg/kg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg/day* every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.
Adjunctive therapy without valproate and with inducers of lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).			
This dosage regimen should be used without valproate but with phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.	0.6 mg/kg/day (two divided doses)	1.2 mg/kg/day (two divided doses)	5–15 mg/kg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day.
Adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation (see «Interaction with other medicinal products and other forms of interaction" section).			

This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1–10 mg/kg/day (once a day or two divided doses). To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day* every one to two weeks until optimal response is achieved, with a maximum of maintenance dose of 200 mg/day.
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see "Interaction with other medicinal products and other forms of interaction" section), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			
If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.			

* If the calculated dose of lamotrigine is less than 25 mg, lamotrigine preparations with the possibility of such a dosage should be used.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.
If epileptic control is achieved with adjunctive treatment, concomitant AEDs may be withdrawn and patients continued on lamotrigine monotherapy.
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 "Special warnings and precautions for use" section). There are no data in children below 1 month of age. Thus, lamotrigine 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 "Pharmacokinetics" and "Special warnings and precautions for use".
Bipolar disorder
The recommended dose escalation and maintenance doses for adults of 18 years of age and above are given in the tables below. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks (see table 4) after which other psychotropic medicinal products and/or AEDs can be withdrawn, if clinically indicated (see table 5). The dose adjustments following addition of other psychotropic medicinal products and/or AEDs are also provided in table 6. Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see "Special warnings and precautions for use» section).

Table 4

Adults aged 18 years and above – recommended dose escalation to the maintenance total daily stabilisation dose in treatment of bipolar disorder

Treatment Regimen	Weeks 1 + 2	Weeks 3 + 4	Week 5	Target Stabilisation Dose (Week 6)*
Monotherapy with lamotrigine or adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).				

This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day (once a day or two divided doses)	200 mg/day – usual target dose for optimal response (once a day or two divided doses). Doses in the range 100–400 mg/day were used in clinical trials.
Adjunctive therapy with valproate (inhibitor of lamotrigine glucuronidation – see "Interaction with other medicinal products and other forms of interaction" section).				
This dosage regimen should be used with valproate regardless of any concomitant medicinal products	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day – usual target dose for optimal response (once a day or two divided doses). Maximum dose of 200 mg/day can be used depending on clinical response.
Adjunctive therapy without valproate and with inducers of lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).				
This dosage regimen should be used without valproate but with phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.	50 mg/day (once a day)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses).
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see "Interaction with other medicinal products and other forms of interaction" section), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.				

* The target stabilisation dose will alter depending on clinical response.

Table 5

Adults aged 18 years and above – maintenance stabilisation total daily dose following withdrawal of concomitant medicinal products in treatment of bipolar disorder.
Once the target daily maintenance stabilisation dose has been achieved, other medicinal products may be withdrawn as shown below.

Treatment Regimen	Current lamotrigine stabilisation dose (prior to withdrawal)	Week 1 (beginning with withdrawal)	Week 2	Week 3 onwards *

<table>
<tr><td colspan="5">Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see “Interaction with other medicinal products and other forms of interaction” section, depending on original dose of lamotrigine).</td></tr>
<tr><td rowspan="2">When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week.</td><td>100 mg/day</td><td>200 mg/day</td><td colspan="2">Maintain this dose (200 mg/day)
(two divided doses)</td></tr>
<tr><td>200 mg/day</td><td>300 mg/day</td><td>400 mg/day</td><td>Maintain this dose (400 mg/day)</td></tr>
<tr><td colspan="5">Withdrawal of inducers of lamotrigine glucuronidation (see “Interaction with other medicinal products and other forms of interaction” section) depending on original dose of lamotrigine.</td></tr>
<tr><td rowspan="3">This dosage regimen should be used when the following are withdrawn:
phenytoin,
carbamazepine,
phenobarbitone,
primidone,
rifampicin,
lopinavir/ritonavir.</td><td>400 mg/day</td><td>400 mg/day</td><td>300 mg/day</td><td>200 mg/day</td></tr>
<tr><td>300 mg/day</td><td>300 mg/day</td><td>225 mg/day</td><td>150 mg/day</td></tr>
<tr><td>200 mg/day</td><td>200 mg/day</td><td>150 mg/day</td><td>100 mg/day</td></tr>
<tr><td colspan="5">Withdrawal of medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see “Interaction with other medicinal products and other forms of interaction” section).</td></tr>
<tr><td>This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn.</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day; two divided doses)
(dose range 100–400 mg/day)</td></tr>
<tr><td colspan="5">In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see “Interaction with other medicinal products and other forms of interaction” section), the treatment regimen recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.</td></tr>
</table>

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

Table 6

Adults aged 18 years and above – adjustment of lamotrigine daily dosing following the addition of other medicinal products in treatment of bipolar disorder.

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

Treatment Regimen	Current lamotrigine stabilisation dose (prior to addition)	Week 1 (beginning with addition)	Week 2	Week 3 onwards
Addition of valproate (inhibitor of lamotrigine glucuronidation – see “Interaction with other medicinal products and other forms of interaction” section) depending on original dose of lamotrigine.				

This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products.	200 mg/day	100 mg/day	Maintain this dose (100 mg/day)	
	300 mg/day	150 mg/day	Maintain this dose (150 mg/day)	
	400 mg/day	200 mg/day	Maintain this dose (200 mg/day)	
Addition of inducers of lamotrigine glucuronidation in patients not taking valproate (see "Interaction with other medicinal products and other forms of interaction" section), depending on original dose of lamotrigine).				
This dosage regimen should be used when the following are added without valproate: phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.	200 mg/day	200 mg/day	300 mg/day	400 mg/day
	150 mg/day	150 mg/day	225 mg/day	300 mg/day
	100 mg/day	100 mg/day	150 mg/day	200 mg/day
Addition of medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation (see "Interaction with other medicinal products and other forms of interaction" section).				
This treatment regimen should be used in case of additional prescribing of other drugs that do not show significant inhibitory or inductive effect on lamotrigine glucuronidation.	Maintain target dose achieved in dose escalation (200 mg/day; dose range 100–400 mg/day).			
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see "Interaction with other medicinal products and other forms of interaction" section), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.				

Discontinuation of lamotrigine in patients with bipolar disorders.

In clinical trials, there was no increase in the incidence, severity or type of adverse reactions following abrupt termination of lamotrigine versus placebo. Therefore, patients may terminate lamotrigine without a step-wise reduction of dose.

Children (below 18 years)

Lamotrigine is not recommended for use in children with bipolar disorders (below 18 years of age) because a randomised withdrawal study demonstrated no significant efficacy and showed increased reporting of suicidality (see "Pharmacodynamics" and "Special warnings and precautions for use" sections).

General dosing recommendations for lamotrigine 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 (e.g. continuous hormonal contraceptives or non-hormonal methods; see "Interaction with other

medicinal products and other forms of interaction" and "Special warnings and precautions for use" sections).

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 "Interaction with other medicinal products and other forms of interaction" and "Special warnings and precautions for use" sections). 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 "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction" sections).

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 "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction" sections). 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 women 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 "Interaction with other medicinal products and other forms of interaction" section).

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 "Interaction with other medicinal products and other forms of interaction" section).

Elderly (above 65 years)

No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from population below 65 years (see "Pharmacokinetics" section).

Renal impairment

Caution should be exercised when administering lamotrigine to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see "Pharmacokinetics" and "Special warnings and precautions for use" sections).

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.

Children.

The effect of lamotrigine as monotherapy for children under 2 years of age or as adjunctive therapy for children under 1 month of age has not been studied. Efficacy and safety of lamotrigine as adjunctive therapy for partial seizures in children aged 1 month to 2 years old have not been established. Therefore, the drug is not recommended for use in children in this age group.

Lamotrigine is not indicated for use in children and adolescents under the age of 18 with bipolar disorder because the efficacy of the drug has not been established and due to an increased risk of suicidal ideation (see "Special warnings and precautions for use" section).

Overdose.

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported, including fatal cases. Overdose has resulted in symptoms including ataxia, nystagmus, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) and QT prolongation have also been observed in overdose patients Broadening of QRS duration to more than 100 msec may be associated with more severe toxicity.

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, taking into account potential effects on cardiac conduction (see "Special warnings and precautions for use" section). Use of intravenous lipid therapy may be considered for treatment of cardiotoxicity that responds insufficiently to sodium bicarbonate. 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 "Pharmacokinetics" section).

Adverse reactions.

Adverse reactions for the indications for the treatment of epilepsy and bipolar disorder, based on available data from controlled clinical trials and other clinical experience, are listed below. Frequency categories were obtained in controlled clinical trials (monotherapy for epilepsy (denoted as †) and bipolar disorder (denoted as §)). If the frequency categories according to clinical data from epilepsy and bipolar disorder are different, the lowest frequency is used. In the absence

of data from controlled clinical trials, frequency categories were derived from other clinical experiences.
The following classification was used to estimate the frequency of adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Skin and subcutaneous tissue disorders: very common – skin rash[5†§]; uncommon – alopecia, photosensitivity reactions; rare – Stevens–Johnson Syndrome[§]; very rare – toxic epidermal necrolysis, drug reaction (or rash) with eosinophilia and systemic symptoms[2].
Blood and lymphatic system disorders: very common – haematological abnormalities[1] (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis), hemophagocytic lymphohistiocytosis (see "Special warnings and precautions for use" section); not known – lymphadenopathy[1], pseudolymphoma.
Immune system disorders: very rare – hypersensitivity syndrome[2], including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi organ failure; not known – hypogammaglobulinemia.
Psychiatric disorders: common – aggression, irritability; very rare – tics (motor and/or phonic tics), hallucinations and confusion, not known – nightmares.
Nervous system disorders: very common – headache[§]; common – somnolence[†§], insomnia[†], dizziness[†§], tremor[†], anxiety[§]; uncommon – ataxia[†]; rare – nystagmus[†], aseptic meningitis (see "Special warnings and precautions for use" section); very rare – unsteadiness, movement disorders, worsening of Parkinson's disease[3], extrapyramidal effects, choreoathetosis[†], increase in seizure frequency.
Eye disorders: uncommon – diplopia[†], blurred vision[†]; rare – conjunctivitis.
Gastrointestinal disorders: rare – nausea[†], vomiting[†], diarrhoea[†], dry mouth[§].
Hepatobiliary disorders: very rare – increased liver function tests, hepatic dysfunction[4], hepatic failure.
Kidneys and urinary system disorders: not known – tubulointerstitial nephritis, tubulointerstitial nephritis syndrome with uveitis.
Musculoskeletal and connective tissue disorders: common – arthralgia[§], very rare – Lupus-like reactions.
General disorders: common – tiredness[†], pain[§], back pain[§].
Description of individual adverse reactions
[1] Haematological abnormalities and lymphadenopathy may or may not be associated with a drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) or hypersensitivity syndrome (see "Special warnings and special precautions for use" and "Immune system disorders" sections).
[2] A rash has also been reported as part of this syndrome, also known as DRESS. This condition was accompanied by a variety of systemic symptoms, including fever, lymphadenopathy, facial edema, abnormal blood parameters, and impaired liver and kidney function. The syndrome can be of varying severity and in rare cases can lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early signs of hypersensitivity (such as fever and lymphadenopathy) may occur even in the absence of a skin rash. If such symptoms occur, the patient should be examined immediately and, in the absence of other causes, lamotrigine should be discontinued.
[3] These reactions have been observed in clinical practice in other clinical conditions.
It was noted that lamotrigine may worsen the symptoms of parkinsonism in patients with Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this condition.
[4] Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.
[5] In adult clinical trials, skin rash was observed in 8–12% of lamotrigine patients and 5–6% of placebo patients. The rash was the reason for drug withdrawal in 2% of patients. The skin rash was

maculopapular in nature, usually occurring within eight weeks of treatment and disappearing after discontinuation of lamotrigine (see “Special warnings and special precautions for use” section). Severe potentially life-threatening skin reactions have been reported, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), and drug reactions with eosinophilia and systemic manifestations (DRESS). Although most patients recover after discontinuation of lamotrigine, some patients retain irreversible scars; in rare cases, these syndromes have led to death (see “Special warnings and special precautions for use” section).

The overall risk of skin rash is apparently closely related to:
- high initial doses of lamotrigine and exceeding the recommended dose regimen during lamotrigine therapy (see “Dosage and administration” section);
- concomitant use of valproate (see “Dosage and administration” section).

It has also been reported that skin rashes are part of the hypersensitivity syndrome, which is accompanied by a variety of systemic symptoms (see “Immune system disorders”).
Decreased bone mineral density, osteopenia, osteoporosis, and fractures have been reported in patients on long-term lamotrigine therapy. The mechanism by which lamotrigine affects bone metabolism has not been determined.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life.
3 years.

Storage conditions.
Store in the original package at the temperature not exceeding 25°C.
Keep out of reach of children.

Package.
10 tablets in a blister. 3 or 6 blisters in a carton package.

Category of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Manufacturer’s location and its address of the place of business.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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