

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Orilam ODT - 25

2. Qualitative and quantitative composition

Each orally disintegrating tablet contains Lamotrigine USP 25mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral dispersible Tablets

4. Clinical particulars

4.1 Therapeutic indications

Epilepsy

Adults and adolescents aged 13 years and above

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

- Seizures associated with Lennox-Gastaut syndrome. Lamotrigine 1 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 generalized 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 1 is not indicated for the acute treatment of manic or depressive episodes.

4.2 Posology and method of administration

Lamotrigine 1 dispersible tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

If the calculated dose of lamotrigine (for example 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.

Restarting therapy

Prescribers should assess the need for escalation to maintenance dose when restarting Lamotrigine 1 in patients who have discontinued Lamotrigine 1 for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine. 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, Lamotrigine 1 should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that Lamotrigine 1 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 and for children and adolescents aged 2 to 12 years are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded.

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.

Table 1: 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 section 4.5):			
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 section 4.5):			
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 section 4.5):			
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 section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

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. There are no data in children below 1 month of age. Thus Lamotrigine 1 is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken.

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 stabilization dose over six weeks after which other psychotropic medicinal products and/or AEDs can be withdrawn, if clinically indicated. The dose adjustments following addition of other psychotropic medicinal products and/or AEDs are also provided below. Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded

Discontinuation of Lamotrigine 1 in patients with bipolar disorder

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 1 without a step-wise reduction of dose.

Children and adolescents below 18 years

Lamotrigine 1 is not recommended for use in children below 18 years of age because a randomized withdrawal study demonstrated no significant efficacy and showed increased reporting of suicidality.

General dosing recommendations for Lamotrigine 1 in special patient populations

Women taking hormonal contraceptives

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. 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 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 a non-elderly adult population.

Renal impairment

Caution should be exercised when administering Lamotrigine 1 to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment.

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.

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 hospitalization 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 (HSS).

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 hospitalization 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 - concomitant use of valproate.

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 Lamotrigine l withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that Lamotrigine l 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 restarted in this patient at any time.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver and aseptic meningitis. 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 l discontinued if an alternative etiology 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.

Clinical worsening and suicide risk

Suicidal ideation and behavior have been reported in patients treated with AEDs in several indications. A meta-analysis of randomized placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behavior. 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 behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior 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 l. Therefore patients receiving Lamotrigine l 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 behavior 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. 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. 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 has 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. 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. However, during prolonged human dosing, lamotrigine did not induce significant changes in the hemoglobin 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

Lamotrigine 1 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 Lamotrigine 1 tablets

Development in children

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

Precautions relating to epilepsy

As with other AEDs, abrupt withdrawal of Lamotrigine 1 may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine 1 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 are 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 behavior in children and adolescents with major depressive disorder and other psychiatric disorders.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

UDP-glucuronyl transferase has 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 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 have little or no effect on the concentration of lamotrigine
Valproate	Atazanavir/ritonavir*	Aripiprazole
	Carbamazepine	Bupropion
	Ethinylestradiol/levonorgestrel combination*	Felbamate
	Lopinavir/ritonavir	Gabapentin
	Phenobarbitone	Lacosamide
	Phenytoin	Levetiracetam
	Primidone	Lithium
	Rifampicin	Olanzapine
		Oxcarbazepine
		Paracetamol
		Perampanel
		Pregabalin
		Topiramate
		Zonisamide

**For dosing guidance

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

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.

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.

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.

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 Cmax 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 a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100-400 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 Cmax and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

In vitro experiments indicated that the formation of lamotrigine primary metabolite, the 2-N-glucuronide, was minimally inhibited by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol or clonazepam. 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

ethinylloestradiol/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. 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.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

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

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.

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.

Data from in vitro assessment demonstrate that lamotrigine, but not the N (2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is a more potent in vitro inhibitor of OCT 2 than cimetidine, with IC₅₀ values of 53.8 μ M and 186 μ M, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

The clinical significance of this has not been clearly defined; however care should be taken in patients co-administered with these medicinal products.

4.6 Pregnancy and Lactation

Pregnancy

Post marketing 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.

If therapy with Lamotrigine 1 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 embryofetal damage by reducing folic acid levels. 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.

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all AED therapy, patients taking Lamotrigine 1 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 1 therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects for epilepsy and bipolar disorder indications are based on available data from controlled clinical studies and other clinical experience and are listed in the table below. Frequency categories are derived from controlled clinical studies (epilepsy monotherapy (identified by †) and bipolar disorder (identified by §)). Where frequency categories differ between clinical trial data from epilepsy and bipolar disorder the most conservative frequency is shown. However, where no controlled clinical trial data are available, frequency categories have been obtained from other clinical experience.

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

System Organ Class	Adverse Event	Frequency
Blood and lymphatic system disorders	Haematological abnormalities ¹ including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis Haemophagocytic lymphohistiocytosis (see section 4.4) Lymphadenopathy ¹ , Pseudolymphoma	Very rare Very rare Not known
Immune System Disorders	Hypersensitivity syndrome ² Hypogammaglobulinaemia	Very rare Not known
Psychiatric Disorders	Aggression, irritability Confusion, hallucinations, tics (motor and/or phonic tics) Nightmares	Common Very rare Not known
Nervous System Disorders	Headache ^{†§} Somnolence ^{†§} , dizziness ^{†§} , tremor [†] , insomnia [†] , agitation [§] Ataxia [†] Nystagmus [†] , aseptic meningitis (see section 4.4) Unsteadiness, movement disorders, worsening of Parkinson's disease ³ , extrapyramidal effects, choreoathetosis [†] , increase in seizure frequency	Very common common Common Uncommon Rare Very rare
Eye disorders	Diplopia [†] , blurred vision [†] Conjunctivitis	Uncommon Rare
Gastrointestinal disorders	Nausea [†] , vomiting [†] , diarrhoea [†] , dry mouth [§]	Common
Hepatobiliary disorders	Hepatic failure, hepatic dysfunction ⁴ , increased liver function tests	Very rare
Skin and subcutaneous tissue disorders	Skin rash ^{5†§} Alopecia, photosensitivity reaction Erythema multiforme, Stevens–Johnson Syndrome [§] Toxic epidermal necrolysis Drug Reaction with Eosinophilia and Systemic symptoms ²	Very common Uncommon Rare Very rare Very rare

Musculoskeletal and connective tissue disorders	Arthralgia [§] Lupus-like reactions	Common Very rare
Renal and urinary disorders	Tubulointerstitial nephritis, tubulointerstitial nephritis and uveitis syndrome	Not known
General disorders and administration site conditions	Tiredness [†] , pain [§] , back pain [§]	Common

Description of selected adverse reactions

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

2 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 Lamotrigine 1 discontinued if an alternative aetiology cannot be established.

3 These effects have been reported during other clinical experience. 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.

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

5 In clinical trials in adults, skin rashes occurred in up to 8-12% of patients taking lamotrigine and in 5-6% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually macropapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamotrigine 1.

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.

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
- concomitant use of valproate.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms. There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with lamotrigine. The mechanism by which lamotrigine affects bone metabolism has not been identified.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via National Pharmacovigilance Electronic Reporting Systems' to the respective National Regulatory Authorities.

4.9 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 nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has 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. There is no experience with hemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour hemodialysis session.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiepileptic's, ATC code: N03AX09.

Mechanism of action

The results of pharmacological studies suggest that lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained repetitive firing of neurones and inhibits release of glutamate (the neurotransmitter which plays a key role in the generation of epileptic seizures). These effects are likely to contribute to the anticonvulsant properties of lamotrigine.

In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

Pharmacodynamic effects

In tests designed to evaluate the central nervous system effects of medicinal products, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from

placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor co-ordination and eye movements, increased body sway and produced subjective sedative effects.

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

5.2 Pharmacokinetic properties

Absorption

Lamotrigine is rapidly and completely absorbed from the gut with no significant first-pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral administration of lamotrigine. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary.

Distribution

Binding to plasma proteins is about 55%; it is very unlikely that displacement from plasma proteins would result in toxicity.

The volume of distribution is 0.92 to 1.22 L/kg.

Biotransformation

UDP-glucuronyl transferase have been identified as the enzymes responsible for metabolism of lamotrigine.

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

Elimination

The apparent plasma clearance in healthy subjects is approximately 30 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of lamotrigine-related material is excreted in faeces. Clearance and half-life are independent of dose. The apparent plasma half-life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population. The half-life of lamotrigine is greatly affected by concomitant medicinal products. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing medicinal products such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone.

Linearity

The pharmacokinetics of lamotrigine are linear up to 450 mg, the highest single dose tested.

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.

Infants aged 2 to 26 months

In 143 Paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of Paediatric patients of 2 to 26 months (47%).

The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher C_{max} levels are likely to be observed in some children with a body weight below 10 kg.

Elderly

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.

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 medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment.

Hepatic impairment

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but reduced foetal weight and retarded skeletal ossification were observed, at exposure levels below or similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to the severity of maternal toxicity, the teratogenic potential of lamotrigine has not been characterized above clinical exposure.

In rats, enhanced foetal as well as post-natal mortality was observed when lamotrigine was administered during late gestation and through the early post-natal period. These effects were observed at the expected clinical exposure.

In juvenile rats, an effect on learning in the Biel maze test, a slight delay in balanopreputial separation and vaginal patency and a decreased postnatal body weight gain in F1 animals were observed at exposures approximately two-times higher than the therapeutic exposures in human adults.

Animal experiments did not reveal impairment of fertility by lamotrigine. Lamotrigine reduced foetal folic acid levels in rats. Folic acid deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC₅₀ was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In

a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose
Colloidal Silicon Dioxide
Croscarmellose Sodium
Aspartame Powder
Crospovidone (Polyplasdone XL-10)
Maltodextrin (Glucidex-12D)
Purified Water
Peppermint DC 117
Magnesium Stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 Months from the date of Manufacturing.

6.4 Special Precautions for storage

Store below 30°C. Keep medicine away from the reach of children

6.5 Nature and Content of container

Packing: 10 tablets are packed in ALU/ ALU Blister.
Such 3 Blister are packed in a printed outer carton along with a pack insert.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder

Micro Labs Limited
No 27, Race Course Road Bangalore-560010.
INDIA

8. Marketing Authorization Number

H2025/CTD8633/16182

9. Date of first authorization/renewal of the authorization

2025 May 26

10. Date of revision of the text

2025 May 26