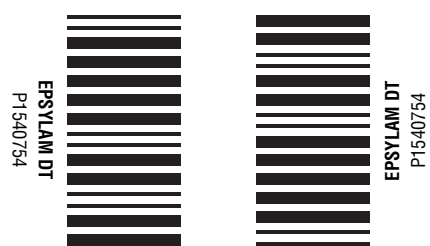


# Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel



## SUMMARY OF PRODUCT CHARACTERISTICS

### EPSYLAM DT (LAMOTRIGINE DISPERSIBLE TABLETS 50 mg and 100 mg)

#### Rx Only

**NAME OF THE MEDICINAL PRODUCT:** Lamotrigine Dispersible Tablets 50 mg  
Lamotrigine Dispersible Tablets 100 mg

**(TRADE) NAME OF PRODUCT:** EPSYLAM DT 50  
EPSYLAM DT 100

#### QUALITATIVE AND QUANTITATIVE COMPOSITION

*Lamotrigine Dispersible Tablets 50 mg*  
Each uncoated tablet contains Lamotrigine 50 mg

*Lamotrigine Dispersible Tablets 100 mg*  
Each uncoated tablet contains Lamotrigine 100 mg

#### PHARMACEUTICAL FORM

*Lamotrigine Dispersible Tablets 50 mg*  
White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '79' on flat side.

*Lamotrigine Dispersible Tablets 100 mg*  
White to off-white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '78' on flat side.

#### PHARMACOLOGICAL PROPERTIES

##### Pharmacodynamics

##### Mechanism of Action

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

##### 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 following administration. Maximum plasma concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics is linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

##### Distribution

Lamotrigine binding to plasma proteins is about 55%. It is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 l/kg.

##### Metabolism

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of Lamotrigine. 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 drugs metabolized by cytochrome P450 enzymes are unlikely to occur.

##### Elimination

The apparent plasma clearance in healthy subjects is approximately 30mL/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 feces. 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).

The half-life of Lamotrigine is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when coadministered with sodium valproate alone.

##### Linearity

The pharmacokinetics of Lamotrigine is linear up to 450mg, the highest single dose tested.

#### CLINICAL PARTICULARS

##### Therapeutic indications

##### Epilepsy

##### Adults

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

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

Lamotrigine is indicated as adjunctive therapy in the treatment of epilepsy, for partial seizures and generalized seizures including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome (above 3 years of age only).

Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended.

After epileptic control has been achieved during adjunctive therapy, concomitant anti epileptic drugs (AEDs) may be withdrawn and patients continued on Lamotrigine monotherapy.

##### Bipolar Disorder

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

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

##### Recommended Dose

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

##### Restarting Therapy

Prescribers should assess the need for escalation to maintenance dose when restarting Lamotrigine in patients who have discontinued Lamotrigine for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for Lamotrigine (see Warning and Precautions). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing Lamotrigine exceeds five half-lives, 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

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other AEDs 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 Medicaments).

##### Dosage in Epilepsy Monotherapy

##### Adults (over 16 years of age) (see Table 1)

The initial Lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of Lamotrigine to achieve the desired response.

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

##### Dosage in Epilepsy Add-On Therapy

##### Adults (over 12 years of age) (see Table 1)

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

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

Thereafter, the dose should be increased by a maximum of 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 to 400 mg/day given in two divided doses.

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

In those patients taking oxcarbazepine without any other inducers or inhibitors of Lamotrigine glucuronidation, the initial Lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is 100 to 200 mg/day given once a day or as two divided doses.

##### Table 1: Recommended treatment regimen in Epilepsy for adults

Treatment regimen	Weeks 1+2	Weeks 3+4	Maintenance Dose
Monotherapy (over 16 years of age)	25 mg (once a day)	50 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks
Add-on therapy with valproate regardless of any concomitant medications (over 12 years of age)	12.5 mg (given 25 mg alternate days)	25 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25 – 50 mg every one to two weeks

Treatment regimen	Weeks 1+2	Weeks 3+4	Maintenance Dose
Add-on Therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments)	50 mg (once a day)	100 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every one to two weeks
	With oxcarbazepine without inducers or inhibitors of Lamotrigine glucuronidation	25 mg (once a day)	50 mg (once a day)
		100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks	
In patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known (see Interaction with Other Medicaments), the treatment regimen as recommended for Lamotrigine with concurrent valproate should be used.			

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

##### Children (2 to 12 years of age) (see Table 2)

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

In those patients taking concomitant AEDs or other medications (see Interaction with Other Medicaments) that induce Lamotrigine glucuronidation with/without other AEDs (except valproate), the initial Lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every one to two weeks until the optimal response is 5 to 15 mg/kg/day given in two divided doses, with a maximum of 400 mg/day.

In patients taking oxcarbazepine without any inducers or inhibitors of Lamotrigine glucuronidation, the initial Lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

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

##### Table 2: Recommended treatment regimen in Epilepsy for children aged 2-12 years (total daily dose in mg/kg bodyweight/day) on combined drug therapy.

Treatment regimen	Weeks 1+2	Weeks 3+4	Maintenance Dose
Add-on therapy with valproate regardless of any concomitant medications	0.15 mg/kg* (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments)	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses) to achieve a maintenance dose of 5-15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.
	With oxcarbazepine without inducers or inhibitors of Lamotrigine glucuronidation	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses) to achieve a maintenance dose of 1-10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known (see Interaction with Other Medicaments), the treatment regimen as recommended for Lamotrigine with concurrent valproate should be used.			
*Where 2 mg tablets are the lowest marketed strength: if the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg Lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then Lamotrigine should not be administered.			
**Where 5 mg tablets are the lowest marketed strength: if the calculated daily dose in patients taking valproate is 2.5 to 5 mg, then 5 mg may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 2.5 mg, then Lamotrigine should not be administered. It is not possible to accurately initiate Lamotrigine therapy using the recommended dosing guidelines in paediatric weighing less than 17 kg.			

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see Warning and Precautions). It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.

##### Children aged less than 2 years

There is insufficient information on the use of Lamotrigine in children aged less than two years.

##### Bipolar Disorder

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

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

Lamotrigine is recommended for use in bipolar patients at risk for a future depressive episode. The following transition regimen should be followed to prevent recurrence of depressive episodes. The transition regimen involves escalating the dose of Lamotrigine to a maintenance stabilization dose over six weeks (see Table 3) after which other psychotropic and/or antiepileptic drugs can be withdrawn, if clinically indicated (see Table 4).

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

##### Table 3: Recommended dose escalation to the maintenance total daily stabilization dose for adults (over 18 years of age) treated for Bipolar Disorder

Treatment Regimen	Weeks 1-2	Weeks 3-4	Weeks 5	Target Stabilization Dose (Week 6)**
a) Adjunct therapy with inhibitors of Lamotrigine glucuronidation e.g. valproate	12.5 mg (given 25 mg Alternate days)	25 mg (once a day)	50 mg (once a day or Two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
a) Adjunct therapy with inhibitors of Lamotrigine glucuronidation e.g. valproate	12.5 mg (given 25 mg Alternate days)	25 mg (once a day)	50 mg (once a day or Two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
b) Adjunct therapy with inducers of Lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate	50 mg (once a day)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments)				

Table 3: Recommended dose escalation to the maintenance total daily stabilization dose for adults (over 18 years of age) treated for Bipolar Disorder

Treatment Regimen	Weeks 1-2	Weeks 3-4	Weeks 5	Target Stabilization Dose (Week 6)**
c) Monotherapy with Lamotrigine Or Adjunctive therapy in patients taking lithium, bupropion, olanzapine, oxcarbazepine, or other agents known not to significantly induce or inhibit Lamotrigine glucuronidation.	25 mg (once a day)	50 mg (once a day or two divided doses)		200 mg (Range 100-400 mg) (once a day or two divided doses)

Note: In patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known, the dose escalation as recommended for Lamotrigine with concurrent valproate, should be used.

\*\*The target stabilization dose will alter depending on clinical response.

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

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

##### b) Adjunct therapy with inducers of Lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate. This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce Lamotrigine glucuronidation (see Interaction with Other Medicaments).

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

##### c) Monotherapy with Lamotrigine or Adjunctive therapy in patients taking lithium, bupropion, olanzapine, oxcarbazepine, or other agents known not to significantly induce or inhibit Lamotrigine glucuronidation.

The initial Lamotrigine dose in patients who are taking lithium, bupropion, olanzapine, oxcarbazepine and are not taking inducers or inhibitors of Lamotrigine glucuronidation or are taking Lamotrigine in monotherapy, is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100 to 400 mg was used in clinical trials.

Once the target daily maintenance stabilization dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule below (see Table 4).

##### Table 4: Maintenance stabilization total daily dose in Bipolar Disorder following withdrawal of concomitant psychotropic or anti-epileptic drugs

Treatment Regimen	Week 1	Week 2	Week 3 onwards*
a) Following withdrawal of inhibitors of Lamotrigine glucuronidation e.g. valproate	Double the stabilization dose, not exceeding 100 mg/week i.e. 100 mg/day target stabilization dose will be increased in week 1 to 200 mg/day		Maintain this dose (200 mg/day) (two divided doses)
b) Following withdrawal of inducers of Lamotrigine glucuronidation depending on original dose. This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments)	400 mg	300 mg	200 mg
	300 mg	225 mg	150 mg
	200 mg	150 mg	100 mg
c) Following withdrawal of other psychotropic or AED drugs in patients not taking significant inducers or inhibitors of Lamotrigine glucuronidation (including lithium, bupropion, olanzapine, oxcarbazepine)	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (Range 100-400 mg)		
Note: In patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known, the treatment regimen recommended for Lamotrigine is to initially maintain the current dose and adjust the Lamotrigine treatment based on clinical response.			

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

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

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

##### b) Following withdrawal of inducers of Lamotrigine glucuronidation depending on original dose. This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone, Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments).

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

##### c) Following withdrawal of other psychotropic or AED drugs with no significant pharmacokinetic interaction with Lamotrigine e.g. lithium, bupropion, olanzapine, oxcarbazepine.

The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

Adjustment of Lamotrigine daily dosing in patients with Bipolar Disorder following addition of other medications There is no clinical experience in adjusting the Lamotrigine daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (see Table 5, below):

##### Table 5: Adjustment of Lamotrigine daily dosing in patients with Bipolar Disorder following the addition of other medications

Treatment Regimen	Current Lamotrigine stabilization dose (mg/day)	Week 1	Week 2	Week 3 onwards
a) Addition of inhibitors of Lamotrigine glucuronidation e.g. valproate, depending on original dose of Lamotrigine	200 mg	100 mg	Maintain this dose (100 mg/day)	
	300 mg	150 mg	Maintain this dose (150 mg/day)	
	400 mg	200 mg	Maintain this dose (200 mg/day)	
b) Addition of inducers of Lamotrigine glucuronidation in patients not taking valproate and depending on original dose of Lamotrigine. This dosage regimen should be used with: phenytoin, carbamazepine,	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
phenobarbitone, primidone, Or with other inducers of Lamotrigine glucuronidation (see Interaction with Other Medicaments).	100 mg	100 mg	150 mg	200 mg
c) Addition of other psychotropic or AED drugs with no significant pharmacokinetic interaction with Lamotrigine e.g. lithium, bupropion, olanzapine, oxcarbazepine.	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
Note: In patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known, the treatment regimen as recommended for Lamotrigine with concurrent valproate, should be used.				

As: 280 x 480 mm Black Booklet Size: 35 x 60 mm

	Product Name	Component	Item Code	Date & Time
	EPSYLAM DT	Leaflet	P1540754	06.10.2025 & 10:10 AM
	Customer / Country	Version No.	Reason Of Issue	Reviewed / Approved by
	Malaysia U3	00	Commercial	
Team Leader	Kiran k	Dimensions	Colours : 01	
Initiator	Arun	280 x 480 mm		
Artis	Designers Ashok	Pharmacode		
		40754	40754	
Additional Information : Supersede Code : P1535768				Sign / Date

#### Discontinuation of Lamotrigine in patients with Bipolar Disorder

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

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

#### General Dosing Recommendations for Lamotrigine in Special Patient Population

##### • Women taking hormonal contraceptives

###### a) Starting Lamotrigine in patients already taking hormonal contraceptives:

Although an oral contraceptive has been shown to increase the clearance of Lamotrigine (see Warning and Precautions and Interaction with Other Medicaments), no adjustment to the recommended dose escalation guidelines for Lamotrigine should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether Lamotrigine is added to valproate (an inhibitor of Lamotrigine glucuronidation), or to an inducer of Lamotrigine glucuronidation, or whether Lamotrigine is added in the absence of valproate or an inducer of Lamotrigine glucuronidation (see Table 1 for epilepsy and Table 3 for bipolar disorder patients).

###### b) Starting 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 twofold (see Warning and Precautions and Interaction with Other Medicaments). 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.

###### c) 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 Warning and Precautions and Interaction with Other Medicaments). It is recommended to gradually decrease the daily dose of Lamotrigine by 50 to 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.

##### • Use with atazanavir/ritonavir

Although atazanavir/ritonavir has been shown to reduce Lamotrigine plasma concentrations (see Interaction with Other Medicaments), no adjustments to the recommended dose escalation guidelines for Lamotrigine should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether Lamotrigine is added to valproate (an inhibitor of Lamotrigine glucuronidation), or to an inducer of Lamotrigine glucuronidation, or whether Lamotrigine is added, or decreased if atazanavir/ritonavir is discontinued.

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

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

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

##### • Renal impairment

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

#### Contraindications

Lamotrigine is contraindicated in individuals with known hypersensitivity to Lamotrigine.

#### Warnings and Precautions

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as 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. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established.

#### Brugada-type ECG

A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using Lamotrigine in patients with Brugada syndrome.

#### 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) and toxic epidermal necrolysis (TEN) (see Side Effects).

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 epileptic children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash and fever during the first eight weeks of therapy. Additionally the overall risk of rash appears to be strongly associated with:

- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy (see Recommended Dose)
- Concomitant use of valproate, (see recommended Dose)

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

All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine withdrawn immediately unless the rash is clearly not drug related. 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.

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

#### Suicide Risk

Symptoms of depression and/or bipolar disorder may occur in patients with epilepsy, and there is evidence that patients with epilepsy and bipolar disorder have an elevated risk for suicidality.

Twenty-five to 50% of patients with bipolar disorder attempt suicide at least once, and may experience worsening of their depressive symptoms and/or the emergency of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including Lamotrigine.

Suicidal ideation and behavior have been reported in patients treated with AEDs in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomized placebo-controlled trials of AEDs (including Lamotrigine) 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 behaviours. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

#### Clinical worsening in bipolar disorder

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 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.

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

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

#### Hormonal contraceptives

##### Effects of hormonal contraceptives on Lamotrigine efficacy:

An ethinylestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of Lamotrigine by approximately two-fold resulting in decreased Lamotrigine levels (see Interaction with Other Medicaments). 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. In women not already taking an inducer of Lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. "pill-free week"), gradual transient increases in Lamotrigine levels will occur during the week of inactive medication.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during Lamotrigine therapy and Lamotrigine dosing adjustments will be needed in most cases.

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

#### Effects of Lamotrigine on hormonal contraceptive efficacy:

Combination of Lamotrigine with hormonal contraceptive (ethinylestradiol/levonorgestrel combination) has shown 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 preparation with Lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

#### Effect of Lamotrigine on organic cationic transporter 2 (OCT 2) substrates

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins. This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Co administration of Lamotrigine with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

#### Dihydrofolate reductase

Lamotrigine is a weak inhibitor of dihydrofolate 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 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 patient with end stage renal failure, plasma concentrations of Lamotrigine were not significantly altered. However, an 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 tablets and dispersible/chewable tablets should not be administered to patients currently being treated with any other preparation containing Lamotrigine without consulting a doctor.

#### 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.

#### Bipolar Disorder

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

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.

#### Interactions with Other Medicaments

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

#### Table 6: Effects of other drugs on glucuronidation of Lamotrigine

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

\*For dosing guidance, see Recommended Dose – General Dosing Recommendations for Lamotrigine in Special Patient Populations.

\*\*Other oral contraceptive and HRT treatments may similarly affect Lamotrigine pharmacokinetic parameters; see Recommended Dose - General Dosing Recommendations for Lamotrigine in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives) and Warning and Precautions – Hormonal Contraceptives.

##### • Interactions involving AEDs (see Recommended Dose)

Valproate, which inhibits the glucuronidation of Lamotrigine, reduces the metabolism of Lamotrigine and increases the mean half life of Lamotrigine nearly two fold. Certain antiepileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the metabolism glucuronidation of Lamotrigine and enhance the metabolism of Lamotrigine.

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

##### • Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on Lamotrigine pharmacokinetics

Serum Lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

Effect of Lamotrigine on hormonal contraceptive pharmacokinetics

The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see Warning and Precautions). The effects of doses of Lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

##### • Interactions involving other medications

Rifampicin increased Lamotrigine clearance and decreased Lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the treatment regimen recommended for Lamotrigine and concurrent glucuronidation inducers should be used (see Recommended Dose).

Lopinavir/ritonavir approximately halved the plasma concentrations of Lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the treatment regimen recommended for Lamotrigine and concurrent glucuronidation inducers should be used (see Recommended Dose).

Atazanavir/ritonavir will reduce the plasma AUC and Cmax of Lamotrigine (see Recommended Dose- General Dosing Recommendations for Lamotrigine in Special Patient Populations).

#### Pregnancy and Lactation

##### PREGNANCY

Women exposed to lamotrigine monotherapy during pregnancy cannot exclude an increased risk of congenital malformations.

In therapy with lamotrigine is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

##### 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.

##### Side Effects

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of Lamotrigine. Adverse reactions identified through post-marketing surveillance are included in the Epilepsy section.

##### Post-marketing

Blood and lymphatic system disorders

Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

##### Epilepsy

Skin and subcutaneous tissue disorders

Very common: Skin rash

Rare: erythema multiforme.

Very Rare: Toxic epidermal necrolysis

The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamotrigine (see Warning and Precautions). Rarely, serious potentially life threatening skin rashes, including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see Warning and Precautions).

The overall risk of rash, appearance to be strongly associated with:

- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy (see Recommended Dose).
- Concomitant use of valproate (see Recommended Dose)

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

#### Blood and lymphatic system disorders

Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions)

#### Immune system disorders

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

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

#### Psychiatric disorders

Common : Aggression, irritability

Very rare : Tics, hallucinations, confusion

#### Nervous system disorders

Very common : Somnolence, ataxia, headache, dizziness.

Common : Nystagmus, tremor, insomnia.

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

#### Eye disorders

Very common : Diplopia, blurred vision

Rare : Conjunctivitis

#### Gastrointestinal disorders

Very common : Nausea, vomiting

Common : Diarrhoea

#### Hepato-biliary disorders

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

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

#### Musculoskeletal and connective tissue disorders

Very rare : Lupus-like reactions.

#### General disorders and administration site conditions

Common : Tiredness

#### Bipolar Disorder

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

#### Skin and subcutaneous tissue disorders

Very common : Skin rash

Rare : erythema multiforme

#### Nervous system disorders

Very common : Headache

Common : Agitation, somnolence, dizziness

#### Musculoskeletal and connective tissue disorders

Common : Arthralgia

#### General disorders and administration site conditions

Common : pain, back pain

#### Symptoms and Treatment of Overdose

##### Symptoms and signs

Acute ingestion of doses in excess of 10 – 20 times the maximum therapeutic dose has been reported. Symptoms of overdose include nystagmus, ataxia, impaired consciousness and coma.

##### Treatment

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal, laxative or gastric lavage) should be performed if indicated. There is no experience with haemodialysis as treatment of overdose.

#### PHARMACEUTICAL PARTICULARS

##### List of excipients

Cellulose Microcrystalline, Magnesium Carbonate, Heavy, Polacrillin Potassium, Sucralose, Povidone, Purified Water, Black Currant Flavour and Magnesium Stearate.

##### Incompatibilities

Not applicable.

##### Shelf life

36 months

##### Special precautions for storage

Store in a dry place below 30°C.

##### Nature and contents of container

EPSYLAM DT are packed in Clear PVC/Aclar- Aluminium foil blister pack, such blisters are packed in printed carton along with pack insert as per market approved packs. i.e. Blister pack of 3x10's and 10x10's.

##### Manufactured by:



#### AUROBINDO

Aurobindo Pharma Limited,

Unit - III, Sy. Nos. 313&314,

Bachupally (V), Bachupally Mandal,

Medchal-Malkajgiri District,

Telangana State, India.

##### Product Registration Holder (PRH),

UNIMED SDN BHD,

No.53, Jalan Tembaga SD 5/2B,

Bandar Sri Damansara,

52200 Kuala Lumpur,

Malaysia.

##### DATE OF REVISION OF THIS LEAFLET

October 2025.