PROFESSIONAL INFORMATION

LAMILEPSY RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LAMILEPSY 25 mg tablets

LAMILEPSY 50 mg tablets

LAMILEPSY 100 mg tablets

LAMILEPSY 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMILEPSY 25 mg: Each tablet contains 25 mg lamotrigine. LAMILEPSY 50 mg: Each tablet contains 50 mg lamotrigine. LAMILEPSY 100 mg: Each tablet contains 100 mg lamotrigine.

LAMILEPSY 200 mg: Each tablet contains 200 mg lamotrigine.

LAMILEPSY contains sugar (lactose monohydrate).

LAMILEPSY 25 mg: Each tablet contains lactose monohydrate 24,70 mg.

LAMILEPSY 50 mg: Each tablet contains lactose monohydrate 49,40 mg.

LAMILEPSY 100 mg: Each tablet contains lactose monohydrate 98,80 mg.

LAMILEPSY 200 mg: Each tablet contains lactose monohydrate 97,60 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LAMILEPSY 25 mg: Beige, round, flat tablets, embossed “MC” with diameter

6,0 mm.

LAMILEPSY 50 mg: Beige, round, flat, scored tablets with diameter 8,0 mm.

LAMILEPSY 100 mg: Beige, round, flat, scored tablets with diameter

9,5 mm.

LAMILEPSY 200 mg: Beige, round, flat, scored tablets with diameter

12,7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children over 12 years

LAMILEPSY is indicated as monotherapy or add-on treatment of partial epilepsy with or without secondary generalized tonic-clonic seizures and in primary generalised tonic-clonic seizures.

Children 2 to 12 years

LAMILEPSY is indicated as add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures not satisfactorily controlled with other antiepileptic medicines.

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Lennox-Gastaut Syndrome

LAMILEPSY is indicated as add-on treatment for seizures associated with Lennox-Gastaut Syndrome.

Bipolar disorder

Adults 18 years of age and over:

LAMILEPSY is indicated for the prevention of mood episodes in patients with bipolar disorder,

predominantly by preventing depressive episodes.

4.2 Posology and method of administration

Strictly adhere to the recommended dosages, especially in combination therapy with valproate where one-tenth to one-fifth of the normal LAMILEPSY dose is used.

Do not exceed the maximum dosage (see section 4.4).

Epilepsy

When concomitant anti-epileptic drugs (AEDs) are withdrawn to achieve LAMILEPSY monotherapy or other AEDs/medicines are added-on to treatment regimens containing LAMILEPSY, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed if weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

Dosage in epilepsy monotherapy

Adults and children over 12 years of age:

Initial dose in monotherapy: 25 mg once daily for two weeks, followed by 50 mg once daily for two weeks. Thereafter, the dosage should be increased by a maximum of 50 mg – 100 mg every 1 – 2 weeks until the optimal response is achieved.

Maintenance dose in monotherapy: The usual dose to achieve optimal response is 100 - 200 mg per day, given in one dose or two divided doses. Some patients have required 500 mg/day of LAMILEPSY to achieve the desired response.

Dosage in epilepsy add-on therapy Adults and children over 12 years of age:

In those patients taking concomitant AEDs or other medicines (see section 4.5) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial dose is 50 mg once a day for two weeks, then 100 mg a day, divided into two doses, for two weeks. The dosage may be increased by a maximum of 100 mg every 1 - 2 weeks until the optimal response is achieved. The usual maintenance dose is 200 - 400 mg/day given in two divided doses.

In those patients taking sodium valproate with/without any other AED, the initial LAMILEPSY dose is 25 mg once every other day for two weeks, then 25 mg once a day for two weeks. The dosage should be increased by a maximum of 25 - 50 mg a day every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 - 200 mg/day given once a day or in two divided doses.

In those patients taking oxcarbazepine 1 200 mg daily, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial LAMILEPSY 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 optimal response is achieved or a dose of 200 mg is reached. The usual maintenance dose to achieve an optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Table 1: Recommended treatment regimen for adults over 12 years of age

Treatment regimen	**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance dose**
Monotherapy	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 medicines	12,5 mg (given as 25 mg on 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
Add on therapy without valproate			
This dosage regimen should be used with: phenytoin, carbamazepine, phenobarbitone, primidone, or with other inducers of lamotrigine glucuronidation (see section 4.5)	50 mg (once a day)	100 mg (two divided doses)	200 - 400 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 section 4.5), the treatment regimen as recommended for LAMILEPSY with concurrent valproate should be used.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see section 4.4).

Children aged 2 to 12 years:

To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

In those patients taking concomitant AEDs or other medicines (see section 4.5) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial LAMILEPSY dose is 0,6 mg/kg body mass/day given in two divided doses for two weeks, followed by 1,2 mg/kg/day 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 achieved. The usual maintenance dose to achieve optimal response is 5 - 15 mg/kg/day given in two divided doses. A maximum daily dose of 400 mg must not be exceeded.

In those patients taking sodium valproate with/without any other AED, the initial LAMILEPSY dose is 0,15 mg/kg body mass/day given once a day for two weeks, followed by 0,3 mg/kg/day given 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 - 5 mg/kg/day given once a day or in two divided doses.

A maximum daily dose of 200 mg must not be exceeded.

In patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial LAMILEPSY 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 an optimal response is achieved, or a dose of 200 mg is reached. 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.

Table 2: Recommended treatment regimen for children aged 2 to 12 years (total daily dose in mg/kg bodyweight/day)**

Treatment regimen	**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance dose**
Add-on therapy with valproate regardless of any concomitant medicines	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 section 4.5)	0,6 mg/kg (two divided doses)	1,2 mg/kg (two divided doses)	1,2 mg/kg increments every one to two weeks 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)	0,6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 - 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for LAMILEPSY with concurrent valproate should be used.			
*If the calculated daily dose in patients taking valproate is 1 - 2 mg, then 2 mg LAMILEPSY may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then LAMILEPSY should not be administered. **If the calculated dose of LAMILEPSY cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet.			

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see section 4.4).

Patients aged 2 - 6 years may require a maintenance dose at the higher end of the recommended range.

Dosage in seizures associated with Lennox-Gastaut Syndrome

The dosing guidelines outlined above for both adults and children aged 2 - 12 years, apply for the treatment of seizures associated with Lennox-Gastaut Syndrome.

Children aged less than 2 years:

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

Therefore, LAMILEPSY is not recommended for use in children under the age of 2.

Bipolar disorder

Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

LAMILEPSY 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 LAMILEPSY to a maintenance stabilisation dose over six weeks (see Table 3), after which other psychotropic and/or AEDs can be withdrawn, if clinically indicated (see Table 4).

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

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

Treatment Regimen	**Week s 1 - 2**	**Weeks 3 - 4**	**Weeks 5 - 6**	**Target stabilisation dose (Week 6) ****

Adjunct therapy with enzyme inhibitors e.g. valproate	12,5 mg (given as 25 mg on 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)
Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking valproate. This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone or, with other inducers of lamotrigine glucuronidation (see section 4.5)	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 dosages)
Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium,	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200 mg (range 100 – 400 mg) (once a day or two divided doses)

bupropion, or monotherapy with LAMILEPSY				
Note: In patients taking AEDs where the pharmacokinetic interaction with LAMILEPSY is currently not known, the dose escalation as recommended for LAMILEPSY with concurrent valproate, should be used.				
**The target stabilisation dose will alter depending on clinical response.				

Adjunct therapy with enzyme inhibitors e.g. valproate

In patients taking enzyme inhibiting concomitant medicines such as valproate, the initial LAMILEPSY dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for 2 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.

Adjunct therapy with enzyme inducers in patients NOT taking inhibitors such as valproate. This dosage regimen should be used with carbamazepine, phenytoin, phenobarbitone, primidone and other medicines known to induce lamotrigine glucuronidation, including lopinavir/ritonavir (see section 4.5)

In those patients taking enzyme inducing medicines such as carbamazepine or phenobarbitone and NOT taking valproate, the initial LAMILEPSY dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 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 in two divided doses which may be given from week 7.

Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, OR monotherapy with LAMILEPSY (see section 4.5)

The initial LAMILEPSY dose in patients taking concomitant medicines with no known/theoretical pharmacokinetic interaction with lamotrigine or in monotherapy, is 25 mg once a day for 2 weeks, followed by 50 mg once a day (or in two divided doses) for 2 weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100 - 400 mg was used in clinical trials with lamotrigine.

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

Table 4: Maintenance stabilisation total daily dose in bipolar disorder following withdrawal of concomitant psychotropic or AEDs

Treatment regimen	**Week 1**	**Week 2**	**Week 3 onwards**
Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate	Double the stabilisation dose, not exceeding 100 mg/week i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day		Maintain this dose (200 mg/day) (two divided doses)
Following withdrawal of adjunct therapy with enzyme inducers depending on	400 mg	300 mg	200 mg
	300 mg	225 mg	150 mg

original maintenance dose. This dosage regimen should be used with: phenytoin, carbamazepine, phenobarbitone primidone or with other inducers of lamotrigine glucuronidation (see section 4.5)	200 mg	150 mg	100 mg
Following withdrawal of adjunct therapy with other psychotropic or AEDs with no known pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion (see section 4.5)	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 LAMILEPSY is currently not known, the dose escalation as recommended for LAMILEPSY with concurrent valproate, should be used.			
*Dose may be increased to 400 mg/day as needed			

Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate

Once valproate has been terminated, the dose of LAMILEPSY should be increased to double the original target stabilisation dose and maintained at this.

Following withdrawal of adjunct therapy with enzyme inducers, depending on original maintenance dose. This regimen should be used with phenytoin, carbamazepine,

phenobarbitone, primidone or other medicines known to induce lamotrigine glucuronidation (see section 4.5) As the enzyme inducer is withdrawn, reduce the dose of LAMILEPSY gradually over 3 weeks.

Following withdrawal of adjunct therapy with other psychotropic or AEDs with no known pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion (see section 4.5)
The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medicine.

Adjustment of LAMILEPSY daily dosing in patients with bipolar disorder following addition of other medicines

There is no clinical experience in adjusting the LAMILEPSY daily dose following the addition of other medicine. However, based on interaction studies, the following recommendations can be made (see Table 5):

Table 5: Adjustment of LAMILEPSY daily dosing in patients with BIPOLAR DISORDER following the addition of other medications

Treatment Regimen	**Current lamotrigine stabilisation dose (mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
Addition of enzyme inhibitors e.g. valproate, depending on original dose of LAMILEPSY	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)	

<table>
<tr><td rowspan="3">Addition of enzyme inducers in patients NOT taking valproate and depending on original dose of LAMILEPSY.
This dosage regimen should be used with: phenytoin carbamazepine, phenobarbitone, primidone or with other inducers of lamotrigine glucuronidation</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>150 mg</td><td>150 mg</td><td>225 mg</td><td>300 mg</td></tr>
<tr><td>100 mg</td><td>100 mg</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>Addition of other psychotropic or AEDs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day)
(range 100 – 400 mg)</td></tr>
<tr><td colspan="5">Note: In patients taking AEDs where the pharmacokinetic interaction with LAMILEPSY is currently not known, the dose escalation as recommended for LAMILEPSY with concurrent valproate, should be used.</td></tr>
</table>

Discontinuation of LAMILEPSY in patients with bipolar disorder There is no increase in the incidence, severity or type of adverse experiences following abrupt termination of LAMILEPSY therefore, patients may terminate LAMILEPSY without a step-wise reduction of dose.

Special populations

Women taking hormonal contraceptives

a) Starting LAMILEPSY in patients already taking hormonal contraceptives:

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see sections 4.4 and 4.5), no adjustments to the recommended dose escalation guidelines for LAMILEPSY should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether LAMILEPSY is added to an inhibitor of lamotrigine glucuronidation e.g. valproate; whether LAMILEPSY is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbitone, primidone or rifampicin; or whether LAMILEPSY is added in the absence of valproate, carbamazepine, phenytoin, phenobarbitone, primidone or rifampicin (see Table 1 for epilepsy and Table 3 for bipolar patients).

b) Starting hormonal contraceptives in patients already taking maintenance doses of LAMILEPSY and NOT taking inducers of lamotrigine glucuronidation: The maintenance dose of LAMILEPSY may need to be increased by as much as two-fold according to the individual clinical response (see sections 4.4 and 4.5).

It is recommended that from the time that the hormonal contraceptive is started, the LAMILEPSY dose is increased by 50 -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 LAMILEPSY and NOT taking inducers of lamotrigine glucuronidation: The maintenance dose of LAMILEPSY may need to be decreased by as much as 50 % according to the individual clinical response (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of LAMILEPSY by 50 - 100 mg each week (at a rate not exceeding 25 % of the total

daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise.

Use with atazanavir/ritonavir

Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (see section 4.5), no adjustments to the recommended dose escalation guidelines for LAMILEPSY should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether LAMILEPSY is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether LAMILEPSY is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

In patients already taking maintenance doses of LAMILEPSY and not taking glucuronidation inducers, the LAMILEPSY dose may need to be increased if atazanavir/ritonavir is added or decreased if atazanavir/ritonavir is discontinued.

Elderly (over 65 years of age)

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 population.

Hepatic impairment

Initial, escalating 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 LAMILEPSY to patients with renal failure. For patients with end-stage renal failure, initial doses of LAMILEPSY should be based on

patients' AED regimen; reduced maintenance doses should be used for patients with significant renal function impairment.

Paediatric population

Children (less than 18 years of age)

Safety and efficacy of LAMILEPSY in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

Method of administration

The tablets may be chewed or swallowed whole with a little water, if preferred.

Missed dose

Doctors should advise patients who forget to take LAMILEPSY to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

LAMILEPSY is contraindicated in the following circumstances:

- Hypersensitivity to lamotrigine or to any of the excipients of LAMILEPSY (see section 6.1).

4.4 Special warnings and precautions for use

Hemophagocytic lymphohistiocytosis (HLH)

LAMILEPSY, containing lamotrigine, can cause a rare but very serious reaction called hemophagocytic lymphohistiocytosis (HLH) which can be life threatening. HLH excessively activates the body's infection-fighting immune system and can cause severe inflammation throughout the body that may lead to hospitalisation and death. HLH typically presents as a persistent fever, usually greater than 38 °C, and it can lead to

severe problems with blood cells and organs throughout the body, such as the liver, kidneys, and lungs.

Symptoms occur generally within 4 weeks of treatment initiation. Early recognition and treatment are important for improving HLH outcomes and reducing mortality. Patients should be advised to seek medical attention if they experience symptoms of HLH. A diagnosis of HLH can be established if a patient presents with at least five of the following eight signs or symptoms: fever and rash, enlarged spleen, cytopenias, elevated levels of triglycerides or low blood levels of fibrinogen, high levels of blood ferritin, haemophagocytosis identified through bone marrow, spleen, or lymph node biopsy, decreased or absent Natural Killer (NK) cell activity and elevated blood levels of CD25 showing prolonged immune cell activation.
LAMILEPSY should be discontinued unless an alternative aetiology can be established.

Cardiac rhythm and conduction abnormalities

In vitro testing showed that lamotrigine, as in DYNA -LAMOLTRIGINE, exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. Lamotrigine, as in LAMILEPSY did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, it could slow ventricular conduction and increase the risk of arrhythmia in people with structural heart disease or myocardial ischemia. Elevated heart rates could also increase the risk of ventricular conduction slowing with LAMILEPSY.
Based on this activity, lamotrigine, as in LAMILEPSY, could slow ventricular conduction (widen QRS) and induce proarrhythmia, including sudden death, in people with structural heart disease or myocardial ischemia.

Therefore, avoid the use of LAMILEPSY in people who have cardiac conduction disorders (e.g., second- or third-degree heart block) ventricular arrhythmias, or cardiac disease or abnormality (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome or other sodium channelopathies). Concomitant use of other sodium channel blockers may increase the risk of proarrhythmia.

Seizures

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of LAMILEPSY.

Patients receiving LAMILEPSY should be closely monitored and changes in hepatic, renal and clotting parameters looked for. Patients should be warned to consult their doctor immediately if rashes or flu-like symptoms associated with hypersensitivity develop, especially within the first month of starting treatment with

LAMILEPSY. Withdrawal of therapy should be considered if unexplained rashes, fever, flu-like symptoms, drowsiness or worsening of seizure control occur.

Dosage recommendations should not be exceeded to minimise the risk of developing rash, requiring withdrawal of therapy. Abrupt withdrawal of LAMILEPSY may provoke rebound seizures.

The risk may be reduced by tapering off the withdrawal of LAMILEPSY over a period of two weeks.

Skin reactions

Adverse skin reactions have been reported, which have generally occurred within the first 8 weeks of starting LAMILEPSY. Although the majority of rashes usually resolve when

LAMILEPSY is discontinued, irreversible scarring and cases of associated death have been reported. A mild rash may subside even with continuation of LAMILEPSY therapy, however, close monitoring is essential. Less frequently, serious and potentially life-threatening skin rashes including Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (HSS) and toxic epidermal necrolysis have been reported, especially in children and in patients using valproate (see section 4.8). Isolated cases have been reported after prolonged treatment (6 months).

The estimated incidence of serious skin rashes in adults is 1 in 1 000. The risk is higher in children than in adults. Some children may require hospitalisation because of the seriousness of skin rashes.

Clinical worsening and suicide risk

There is evidence that patients with bipolar disorder and with epilepsy, have an elevated risk for suicidality. This risk may continue during treatment.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines (AEDs), including LAMILEPSY in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEDs (including LAMILEPSY) has also shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

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

The possibility of a suicide attempt is inherent in bipolar disorder, and close supervision of high-risk patients should accompany therapy with LAMILEPSY.

Worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medicines for bipolar disorder, including lamotrigine. Therefore, patients

taking LAMILEPSY for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts.

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

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing LAMILEPSY, 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 LAMILEPSY efficacy:

An ethinyloestradiol / levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine, as in LAMILEPSY, by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5).

Higher maintenance doses of LAMILEPSY (by as much as two-fold) may be needed to attain an optimum therapeutic response after titration. In women that are not already taking an inducer of LAMILEPSY glucuronidation and taking a hormonal contraceptive that includes one week of inactive medicine (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medicine. These

increases will be greater when LAMILEPSY dose increases are made in the days before or during the week of inactive contraceptive medicine. Breakthrough convulsions in women also using hormonal contraceptives could occur (see section 4.2).

Healthcare providers should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during LAMILEPSY therapy, and LAMILEPSY dosing adjustments may be needed. Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect LAMILEPSY pharmacokinetic parameters.

Effects of LAMILEPSY on hormonal contraceptive efficacy:

When LAMILEPSY and a hormonal contraceptive (ethinylestradiol / levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, these changes may result in decreased contraceptive efficacy in patients taking hormonal preparations. Cases of unplanned pregnancy, metro/menorrhagia, breakthrough bleeding and amenorrhoea have been reported, therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Effect of LAMILEPSY on organic cationic transporter 2 (OCT 2) substrates

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (see section 4.5). This may result in increased plasma levels of certain medicines that are substantially excreted via this route. Co- administration of LAMILEPSY with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

Dihydrofolate reductase

LAMILEPSY inhibits dihydrofolate reductase and should be used with caution with other folate antagonists during long term therapy. However, during prolonged human dosing of up to 1

year, LAMILEPSY did not induce significant changes in haemoglobin concentration, mean corpuscular volume, serum or red blood cell folate concentrations.

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 medicines containing lamotrigine

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

Information on excipients of LAMILEPSY

LAMILEPSY contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LAMILEPSY.

LAMILEPSY contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Paediatric population

The weight of a child must be monitored and the dose reviewed as weight changes occur. If the dose calculated for children, according to bodyweight, does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

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

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

- high initial doses of LAMILEPSY and exceeding the recommended dose escalation of LAMILEPSY (see section 4.2)
- concomitant use of valproate, which increases the mean half-life of LAMILEPSY nearly two-fold (see sections 5.2 and 4.2).

As it cannot be predicted reliably which rashes will prove to be life-threatening, all patients (adults and children) who develop a rash should be promptly evaluated and LAMILEPSY withdrawn immediately unless the rash is clearly not related to the medicine. Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, pruritus, facial oedema, abnormalities of the blood and liver, and thrombocytopenia. The syndrome shows a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multi-organ failure. It is important 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 LAMILEPSY therapy discontinued if an alternative aetiology cannot be immediately established.

Aseptic meningitis was reversible on withdrawal of the LAMILEPSY in most cases but recurred in a number of cases on re-exposure to LAMILEPSY. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. LAMILEPSY should not be restarted in patients who have discontinued due to aseptic meningitis associated with treatment 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 behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. LAMILEPSY should not be used in children and adolescents with bipolar disorder.

4.5 Interaction with other medicines and other forms of interaction Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicines that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine. There is no evidence that LAMILEPSY causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. LAMILEPSY may induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

Those medicines that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in the table below. Specific dosing guidance for these medicines is provided in section 4.2. In addition, this table lists those medicines which have been shown to have little or no effect on the concentration of lamotrigine. Co-administration of such medicines would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Effects of medicines on the concentration of lamotrigine

Medicines that increase the concentration of lamotrigine (doubling of lamotrigine half-life)	**Medicines that decrease the concentration of lamotrigine (halving lamotrigine half-life)**	**Medicines have little or no effect on the concentration of lamotrigine**
Valproate	Atazanavir/ritonavir* Carbamazepine Ethinyloestradiol/ levonorgestrel combination ** Phenytoin Phenobarbitone Phenytoin Primidone Rifampicin	Aripiprazole Bupropion Felbamate Gabapentin Oxcarbazepine Lacosamide Levetiracetam Lithium Olanzapine Paracetamol Perampanel Topiramate Pregabalin Zonisamide
* For dosing guidance, refer to section 4.2 Special Populations ** Special Patient Populations, for women taking hormonal contraceptives also see section 4.4 – Hormonal Contraceptives.		

Interactions involving AEDs (see section 4.2)

Concomitant use of valproic acid significantly reduces the metabolism of lamotrigine and increases the half-life and plasma concentrations of lamotrigine, nearly two-fold, due to competition for hepatic glucuronidation. Plasma concentrations of valproic acid

may decrease slightly when LAMILEPSY is added (see section 5.2).

Enzyme-inducing medicines (such as phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir and atazanavir/ritonavir) significantly enhance the metabolism of LAMILEPSY leading to an increased clearance and subsequent reduction of the elimination half-life of lamotrigine, as in LAMILEPSY.

Central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea have been reported in patients taking carbamazepine following the introduction of lamotrigine, as in LAMILEPSY. On reduction of the dose of carbamazepine, these events usually resolve. Although a similar effect was observed during a study of lamotrigine and oxcarbazepine, dose reduction was not investigated.

Decreased lamotrigine levels have been reported 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, the treatment regimen for lamotrigine adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation should be used in patients receiving concomitant therapy with oxcarbazepine.

Co-administration of felbamate (1 200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine in a study of healthy volunteers.

Retrospective analysis of plasma levels in patients receiving lamotrigine both with and without gabapentin, indicates gabapentin does not appear to change the apparent clearance of lamotrigine.

Evaluation of serum concentrations of both levetiracetam and lamotrigine, when taken concomitantly, 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.

Whilst 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, co-administration of zonisamide (200 - 400 mg/day) with lamotrigine (150 - 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10 %. An effect of this magnitude is not considered to be clinically relevant.

Interactions involving other psychotropic 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 only had 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. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

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

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (≥ 100 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7-day period and continued once daily for a further 7 days. An average reduction of approximately 10 % in Cmax and AUC of lamotrigine was observed.

In vitro inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsomes suggested that lamotrigine does not reduce the clearance of medicines eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on the pharmacokinetics of LAMILPSY:

30 µg ethinylestradiol / 150 µg levonorgestrel in a combined oral contraceptive pill has shown an approximately two-fold increase in lamotrigine, as in LAMILEPSY, oral clearance, resulting

in an average 52 % and 39 % reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations gradually increase during the course of the week of inactive medicine (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medicine being, on average, approximately two-fold higher than during co-therapy. Breakthrough seizures have been reported in women using contraceptives.

Effect of LAMILEPSY on hormonal contraceptive pharmacokinetics:

A steady state dose of 300 mg LAMILEPSY has shown no effect on the pharmacokinetics of the ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component is observed, resulting in an average 19 % and 12 % reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and oestradiol indicates some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicates that there is no hormonal evidence of ovulation. The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of LAMILEPSY other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted. Cases of unplanned pregnancy, menstrual disorders and amenorrhoea have been reported. Patients should be instructed to report any changes in their menstrual bleeding patterns.

LAMILEPSY inhibits dihydrofolate reductase and should be used with caution with other folate antagonists.

Interactions involving other medicines

Although there are no formal interaction studies, it has been reported that rifampicin increases lamotrigine clearance and decreases lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation (as per a study in 10 male volunteers). In patients receiving concomitant therapy with rifampicin, the treatment regimen recommended for LAMILEPSY and concurrent glucuronidation inducers should

be used (see section 4.2).

Lopinavir/ritonavir approximately halves the plasma concentrations of lamotrigine, probably by induction of glucuronidation as shown in a study in healthy volunteers. In patients receiving concomitant therapy with lopinavir/ritonavir, the treatment regimen recommended for LAMILEPSY and concurrent glucuronidation inducers should be used (see section 4.2).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32 % and 6 %, respectively (see section 4.2 – sub-section Special Populations).

In a study in healthy adult volunteers, paracetamol 1g (four times daily) reduced the plasma AUC and Cmin of lamotrigine by an average of 20 % and 25 %, respectively.

Data from *in vitro* assessment demonstrate that lamotrigine, but not the 2-N-glucuronide metabolite, is an inhibitor of Organic Transporter 2 (OCT 2) at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC50 value of 53,8 µM. Co-administration of lamotrigine with renally excreted medicines, which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicines products. The clinical significance of this has not been clearly defined, however care should be taken in patients co administered with these medicines.

Interactions involving laboratory tests

Lamotrigine has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for phencyclidine (PCP). A more specific alternative chemical method should be used to confirm a positive result.

4.6 Fertility, pregnancy and lactation

The safety of LAMILEPSY in pregnancy and lactation has not been established.

Pregnancy

There is some evidence of an increased risk of oral cleft malformations following exposure to lamotrigine in pregnancy.

The decision to use LAMILEPSY during pregnancy should be taken by the physician following assessment of the benefit / risk profile.

A large amount of data on pregnant women exposed to lamotrigine monotherapy during the first trimester of pregnancy (more than 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts. Animal studies have shown developmental toxicity.

If therapy with LAMILEPSY is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels. 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.

Breastfeeding

The decision to breastfeed should be taken by the mother in consultation with the physician.

The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.

There is limited information on the use of LAMILEPSY in lactation. LAMILEPSY passes into breast milk in concentrations usually of the order of 40 % - 60 % of the serum concentration.

In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur.

4.7 Effects on ability to drive and use machines

LAMILEPSY may have a minor influence on the ability to perform tasks requiring concentration and coordination.

LAMILEPSY has adverse events of a neurological character such as dizziness and diplopia. Therefore, patients should see how LAMILEPSY therapy affects them before driving or operating machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions **Epilepsy**

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Blood dyscrasias including aplastic anaemia, eosinophilia, leucopenia, thrombocytopenia, agranulocytosis, neutropenia, red cell aplasia, pancytopenia
	Frequency unknown	Bone marrow depression, septic

		shock, hemophagocytic lymphohistiocytosis (HLH)*
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity syndrome, lymphadenopathy, disseminated intravascular coagulation, multi-organ failure Hypogammaglobinaemia*
Psychiatric disorders	Frequent Less frequent Frequency unknown	Aggression, irritability Hallucinations, tics, confusion Nightmares*
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache, insomnia, dizziness, drowsiness, tremor, coordination abnormalities, paraesthesia, vertigo Ataxia Anxiety, depression, amnesia, slurred speech, agitation, extrapyramidal effects, choreoathetosis, aseptic meningitis*, unsteadiness*, movement disorders*, worsening of the disease*, worsening of Parkinson's disease*, increase in seizure frequency in epilepsy only*

Eye disorders	Frequent Less frequent Frequency unknown	Vision abnormalities, blurred vision, diplopia Nystagmus Conjunctivitis*
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Angioedema (trouble in breathing, swelling of face, mouth, hands or feet), rhinitis, apnoea, oesophagitis Interstitial pneumonitis with pulmonary infiltrates
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting Constipation, diarrhoea, dyspepsia
Hepatobiliary disorders	Less frequent	Increased liver function tests, hepatic failure, hepatic dysfunction
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Severe skin rashes, skin rash Stevens-Johnson syndrome, toxic epidermal necrolysis especially in children, erythema multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Maculopapular skin rash, alopecia*
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Arthralgia Asthenia, pain, lupus-like reactions Low bone mineral density and reduced bone formation,

		rhabdomyolysis, short-stature
Renal and urinary disorders	Frequency unknown	Tubulointerstitial nephritis*, tubulointerstitial nephritis and uveitis syndrome*
General disorders and administrative site conditions	Frequent Less frequent	Unnatural weight loss, tiredness, back pain, dryness of the mouth Fever, malaise, flu-like symptoms, photosensitivity

Bipolar disorder

The side effects below should be considered alongside those in epilepsy for an overall safety profile of LAMILEPSY.

System Organ Class	**Frequency**	**Side effects**
Nervous system disorders	Frequent	Headache, agitation, somnolence, dizziness
Skin and subcutaneous tissue disorders	Frequent Less frequent	Skin rashes Stevens-Johnson syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia
General disorders and administrative site conditions	Frequent	Pain, back pain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is

important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose of LAMILEPSY 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 milliseconds may be associated with more severe toxicity.

Management of overdose

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy.

Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics

ATC code: N03AX09

Pharmacological classification: A.2.5 Anticonvulsants, including anti-epileptics

Mechanism of action

In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease lamotrigine could potentially slow ventricular conduction (widen QRS) and induce pro-dysrhythmia.

Lamotrigine blocks voltage-sensitive sodium channels, thereby stabilising neuronal membranes and inhibiting neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a major role in the generation of epileptic seizures.

5.2 Pharmacokinetic properties

Absorption:

Lamotrigine is well and completely absorbed from the gut. The absorption is unaffected by food. The time to peak concentration is 2,5 hours.

Distribution:

Lamotrigine is moderately (55 %) bound to plasma proteins.

Biotransformation:

Following multiple administration of lamotrigine (150 mg twice daily), there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state.

Elimination:

The mean elimination half-life is 24 - 30 hours. The half-life of lamotrigine is affected by concomitant use of enzyme-inducing medicines such as phenytoin, carbamazepine, phenobarbitone or primidone, with a mean value of approximately 14 hours.

The half-life of lamotrigine increases to approximately 70 hours when co-administered with valproic acid alone (see section 4.2).

Clearance adjusted for bodyweight is higher in children aged 12 years and under, than in adults, with the highest values in children under 5 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-indicating medicines such as carbamazepine and phenytoin.

Linearity/non-linearity:

The pharmacokinetic profile is linear up to 450 mg, the highest single dose tested.

Pharmacokinetics in special patient groups

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 clinical 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 9 studies with non-elderly adults after single dose of 30 to 450 mg.

Renal impairment

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were given a single 100 mg dose of lamotrigine. Mean CL/F were 0, 42

mL /min/kg (between haemodialysis) and 1,57 mL /min/kg (during haemodialysis) compared to 0,58 mL /min/kg in healthy volunteers. Mean plasma half-lives were 42,9 hours (chronic renal failure) 57,4 hours (between haemodialysis) and 13, 0 hours (during haemodialysis), compared to 26, 2 hours in healthy volunteers. On average, approximately 20 % (range = 5, 8 to 35, 1) of the amount of lamotrigine present in the body was eliminated during a 4 hour haemodialysis session. For this patient population, initial dose of lamotrigine should be based in patients antiepileptic drug (AED) regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see section 4.2).

Hepatic impairment

A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as control. The median apparent clearance of lamotrigine was 0,31, 0,24 and 0,10 ml/min/kg in patients with grade A, B or C (Child-Plough Classification) Hepatic impairment, respectively, compared to 0,34 ml/min/kg in healthy controls. Reduced doses should be used in patients with grade B or C hepatic impairment (see section 4.2).

Paediatric population

Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children under 5 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-indicating medicines such as carbamazepine and phenytoin.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Iron oxide yellow E172

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in the original pack.

Protect against moisture and light.

Do not remove the blisters from the outer carton until required for use.

6.5 Nature and contents of container

LAMILEPSY 25 mg, 50 mg, 100 mg and 200 mg are packed into PVC/Aluminium blister packs of 60 tablets in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town 7945,

South Africa

8. REGISTRATION NUMBER(S)

LAMILEPSY 25 mg: A40/2.5/0173

LAMILEPSY 50 mg: A40/2.5/0169

LAMILEPSY 100 mg: A40/2.5/0166

LAMILEPSY 200 mg: A40/2.5/0167

9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

19 May 2023

NAMIBIA:

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LAMILEPSY 50 mg: NAM NS2 08/2.5/0178

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LAMILEPSY 200 mg: NAM NS2 08/2.5/0180