SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LAMITOR 25, Tablets.

LAMITOR 50, Tablets.

LAMITOR 100, Tablets.

LAMITOR 200, Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMITOR 25: Each tablet contains 25 mg lamotrigine

Contains lactose monohydrate (48,75 mg/tablet)

LAMITOR 50: Each tablet contains 50 mg lamotrigine

Contains lactose monohydrate (97,50 mg/tablet)

LAMITOR 100: Each tablet contains 100 mg lamotrigine

Contains lactose monohydrate (195 mg/tablet)

LAMITOR 200: Each tablet contains 200 mg lamotrigine

Contains lactose monohydrate (390 mg/tablet)

For the full list of excipients (see section 6.1).

3. PHARMACEUTICAL FORM

Tablets.

LAMITOR 25: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side.

LAMITOR 50: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side.

LAMITOR 100: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side.

LAMITOR 200: Light yellow coloured, round, flat uncoated tablets, with bisecting line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EPILEPSY:

Adults and children over 12 years

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

Children 2 to 12 years

LAMITOR 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

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

BIPOLAR DISORDER (Adults 18 years of age and over):

LAMITOR 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

General Dosing Recommendations:

It is important to adhere to the recommended dosages especially in combination therapy with valproate where one-tenth of the normal dose is used.

Do not exceed the maximum dosage (see section 4.4). To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed if necessary. 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.

Restarting Therapy:

Prescribers should assess the need for escalation to maintenance dose when restarting LAMITOR in patients who have discontinued LAMITOR for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for LAMITOR (see section 4.4). 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 LAMITOR exceeds five half-lives (see section 5.2), LAMITOR should generally be escalated to the maintenance dose according to the appropriate schedule. It is recommended that LAMITOR not be restarted in patients who have discontinued due to rash associated with prior treatment with LAMITOR.

EPILEPSY:

When concomitant antiepileptic medicines are withdrawn to achieve LAMITOR monotherapy or other AEDs/medications are added-on to treatment regimens containing LAMITOR, 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 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.

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. The dosage may be increased by a maximum of 50 to 100 mg every 1 to 2 weeks until the optimal response is achieved.

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

Dosage in epilepsy add-on therapy:

Adults and children over 12 years of age

In those patients taking concomitant antiepileptic medicines (AEDs) or other medicines (see section 4.4) that induce lamotrigine glucorinidation 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 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 200 to 400 mg/day given in two divided doses.

In those patients taking sodium valproate with/without any other AED: The initial dose is 25 mg once every other day for two weeks, then 25 mg once a day for two weeks. The dosage may be increased by a

maximum of 25 to 50 mg a day every 1 or 2 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 oxcarbazepine 1200 mg daily, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial LAMITOR dose is 25 mg once a day for 2 weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to100 mg every 1 to 2 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.

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 to 200 mg (Once a day or two divided doses) To achieve maintenance, doses may be increased by 50 to 100 mg every 1 to 2 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 to 200 mg (Once a day or two divided doses) To achieve maintenance, doses may be increased by 25 to 50 mg every 1 to 2 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 to 400 mg (Two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks

	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	25 mg (Once a day)	50 mg (Once a day)	100 to 200 mg (Once a day or two divided doses) To achieve maintenance, doses may be increased by 50 to 100 mg every 1 to 2 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 LAMITOR 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

The initial LAMITOR dose in those children not taking sodium valproate:

In those patients taking concomitant AEDs or other medicines (see section 4.4) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), The initial dose is 0,6 mg/kg body-weight daily given in two divided doses for two weeks, followed by 1,2 mg/kg daily in 2 divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1,2 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 5 to 15 mg/kg/day given in two divided doses. A maximum daily dose of 400 mg must not be exceeded.

In those children taking sodium valproate with/without any other AED: The initial dose of 0,15 mg/kg once daily for two weeks, followed by 0,3 mg/kg once daily for two weeks. Thereafter the dose is increased by a maximum of 0,3 mg/kg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 1 to 5 mg/kg, which may be 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 LAMITOR dose is 0,3 mg/kg bodyweight/day given once a day or in two divided doses for 2 weeks, followed by 0,6 mg/kg/day given once a day or in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,6 mg/kg every 1 to 2 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.

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

<table>
<tr><th colspan="2">Treatment regimen</th><th>Weeks 1 + 2</th><th>Weeks 3 + 4</th><th>Maintenance Dose</th></tr>
<tr><td colspan="2">Add-on therapy with valproate regardless of any other concomitant medicine</td><td>0,15 mg/kg* (Once a day)</td><td>0,3 mg/kg (Once a day)</td><td>0,3 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 1 to 5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.</td></tr>
<tr><td rowspan="2">Add-on therapy without valproate</td><td>This dosage regimen should be used with: Phenytoin, Carbamazepine, Phenobarbitone, Primidone, or with other inducers of lamotrigine glucuronidation (see section 4.5).</td><td>0,6 mg/kg (two divided doses)</td><td>1,2 mg/kg (two divided doses)</td><td>1,2 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 5 to 15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.</td></tr>
<tr><td>With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation</td><td>0,3 mg/kg (one or two divided doses)</td><td>0,6 mg/kg (one or two divided doses)</td><td>0,6 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 1 to 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.</td></tr>
<tr><td colspan="5">In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for LAMITOR with concurrent valproate should be used.</td></tr>
<tr><td colspan="5">* If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg LAMITOR may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then LAMITOR should not be administered.</td></tr>
</table>

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

Note: If the calculated daily dose is 2,5 to 5 mg, then 5 mg LAMITOR may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 2,5 mg, then LAMITOR should not be administered.

Patients aged 2 to 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 to 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 LAMITOR in children aged less than two years.

BIPOLAR DISORDER:

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

LAMITOR 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 LAMITOR to a maintenance stabilisation dose over 6 weeks (see table below) after which other psychotropic and/or anti- epileptic medicines can be withdrawn, if clinically indicated. Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with LAMITOR in mania has not been conclusively established

Recommended dose escalation to the maintenance total daily stabilisation dose for adults (over 18 years of age) treated for bipolar disorder:

Treatment Regimen	**Weeks 1 to 2**	**Weeks 3 to 4**	**Week 5**	**Target Stabilisation Dose (Week 6) ****
a) Adjunct therapy with enzyme inhibitors 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 enzyme inducers e.g., carbamazepine and phenobarbitone in patients NOT taking 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)
c) Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g., lithium, bupropion, OR monotherapy with lamotrigine	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 to 400 mg) (once a day or two divided doses)
NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMITOR is currently not known, the dose escalation as recommended for LAMITOR with concurrent valproate, should be used.				
**The Target stabilisation dose will alter depending on clinical response.				

a) Adjunct therapy with enzyme inhibitors e.g., valproate:

In patients taking enzyme inhibiting concomitant medicines such as valproate the initial LAMITOR dose is 25 mg every alternate day for 2 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.

b) Adjunct therapy with enzyme inducers e.g., carbamazepine and phenobarbitone in patients NOT taking valproate:

In those patients taking enzyme inducing medicines such as carbamazepine or phenobarbitone and NOT taking valproate, the initial LAMITOR 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 given in two divided doses which may be given from week 7.

c) Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g., lithium, bupropion, OR monotherapy with LAMITOR:

The initial LAMITOR 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 to 400 mg was used in trails.

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

Maintenance stabilisation total daily dose in bipolar disorder following withdrawal of concomitant psychotropic or anti-epileptic medicines:

<table>
<tr><th>Treatment Regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td>a) Following withdrawal of enzyme inhibitors e.g., valproate</td><td>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</td><td colspan="2">Maintain this dose (200 mg/day) (two divided doses)</td></tr>
<tr><td rowspan="3">b) Following withdrawal of enzyme inducers e.g., carbamazepine depending on original dose</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>c) Following withdrawal of other psychotropic or AED medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g., lithium, bupropion</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 to 400 mg)</td></tr>
<tr><td colspan="4">NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMITOR is currently not known, the dose escalation as recommended for LAMITOR with concurrent valproate, should be used.</td></tr>
<tr><td colspan="4">* Dose may be increased to 400 mg/day as needed</td></tr>
</table>

a) Following withdrawal of adjunct therapy with enzyme inhibitors e.g., valproate:

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

b) Following withdrawal of adjunct therapy with enzyme inducers e.g., carbamazepine, depending on original maintenance dose:

The dose of LAMITOR should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

c) Following withdrawal of adjunct therapy with other psychotropic or anti-epileptic medicines with no known pharmacokinetic interaction with lamotrigine e.g., lithium, bupropion:

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

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

There is no clinical experience in adjusting the LAMITOR daily dose following the addition of other medicines. However, based on drug interaction studies, the following recommendations can be made (see below):

Adjustment of LAMITOR daily dosing in patients with bipolar disorder following the addition of other medicines:

Treatment Regimen	**Current lamotrigine stabilisation dose mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
a) Addition of enzyme inhibitors e.g., valproate, depending on original dose of LAMITOR	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 enzyme inducers e.g., carbamazepine in patients NOT taking valproate and depending on original dose of LAMITOR	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
c) Addition of other psychotropic or AED medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g., lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (range 100 to 400 mg)			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with LAMITOR is currently not known, the dose escalation as recommended for LAMITOR with concurrent valproate, should be used.				

Discontinuation of LAMITOR in patients with bipolar disorder: In studies, there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of LAMITOR versus placebo. Therefore, patients may terminate LAMITOR without a step-wise reduction of dose.

Children (less than 18 years of age): Safety and efficacy of LAMITOR in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

General Dosing recommendations for LAMITOR in Special Patient Populations:

Women taking hormonal contraceptives:

(a) Starting LAMITOR in patients already taking hormonal contraceptives*:*

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

(b) Starting hormonal contraceptives in patients already taking maintenance doses of LAMITOR and NOT taking inducers of lamotrigine glucuronidation:

The maintenance dose of LAMITOR may need to be increased by as much as two-fold according to the individual clinical response (see section 4.4 and 4.5).

(c) Stopping hormonal contraceptives in patients already taking maintenance doses of LAMITOR and NOT taking inducers of lamotrigine glucuronidation:

The maintenance dose of LAMITOR may need to be decreased by as much as 50 % according to the individual clinical response (see section 4.4).

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, 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 LAMITOR to patients with renal failure. For patients with end-stage renal failure, initial doses of LAMITOR should be based on patient's AED regimen; reduced maintenance doses should be used for patients with significant renal functional impairment.

Method of administration:

Orally, LAMITOR tablets should be swallowed whole with water.

4.3 Contraindications

LAMITOR is contraindicated in the following circumstances:

- Individuals with a known hypersensitivity to the active substance (lamotrigine) or to any other components of the formulation (see section 6.1).

4.4 Special warnings and precautions for use

Cardiac rhythm and conduction abnormalities

LAMITOR can increase the risk of serious arrhythmias, which can be life-threatening, in patients with clinically important structural or functional heart disorders. The mechanism of the cardiac concern of LAMITOR is not clearly understood, but attributed from its sodium channel blocking properties. This is because the inhibition of the cardiac sodium channels can prolong the QRS complex, a phenomenon associated with increased mortality in patients with underlying cardiovascular disease.

Brugada-type ECG

Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine. The use of lamotrigine should be carefully considered in patients with Brugada syndrome.

Skin reactions

Adverse skin reactions have been reported, which have generally occurred within the first eight weeks starting LAMITOR. Although the majority of rashes usually resolve when LAMITOR is discontinued, irreversible scarring and cases of associated death have been reported. A mild rash may subside even with continuation of LAMITOR therapy; however, close monitoring is essential. Less frequently, serious and potentially life-threatening skin rashes including Stevens-Johnson syndrome 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).

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

The risk of serious skin rashes in children is higher than in adults.

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

- High initial doses of LAMITOR and exceeding the recommended dose escalation of LAMITOR (see section 4.2).
- Concomitant use of valproate, which increases the mean half-life of LAMITOR nearly two-fold (see section 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 LAMITOR withdrawn immediately unless the rash is clearly not medicine related.

If the patient has developed Stevens-Johnson syndrome *(*SJS), Toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with the use of lamotrigine, treatment with lamotrigine must not be re-started in this patient at any time.

Rash has also been reported as part of DRESS: also known as hypersensitivity syndrome 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 multiorgan 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 LAMITOR therapy discontinued if an alternative aetiology cannot be immediately established.

Haemophagocytic lymphohistiocytosis (HLH)

HLH is characterised by signs and symptoms, like fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation, HLH can be life threatening.

Patients should be informed of the symptoms associated with HLH and should be advised to seek medical attention immediately if they experience these symptoms while on lamotrigine therapy.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be promptly discontinued unless an alternative aetiology can be established.

Clinical worsening and suicide risk

Suicidal ideation and behaviour in patients treated with AEDs in several indications. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

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

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels. A decrease in lamotrigine levels has been associated with loss of seizure control.

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

The interaction between other oral contraceptive or HRT treatments and lamotrigine have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy

Lamotrigine and a hormonal contraceptive (ethinyloestradiol / levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH. The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern, i.e., breakthrough bleeding.

Dihydrofolatereductase

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and should be used with caution with other folate antagonists, 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 single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

Patients taking other preparations containing Lamotrigine

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

Excipients

LAMITOR contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

Development in children

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

Precautions relating to epilepsy

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

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.

Patients receiving LAMITOR should be closely monitored and changes in hepatic, renal and clotting parameters looked for. Patients should be warned to consult their doctors immediately if rashes or flu-like symptoms associated with hypersensitivity develop, especially within the first month of starting treatment with LAMITOR. Withdrawal of LAMITOR therapy should be considered if unexplained rashes, fever, flu-like symptoms, drowsiness or worsening of seizure control occur.

Myoclonic seizures may be worsened by lamotrigine.

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

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

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.

Precautions related to bipolar disorder

Children and adolescents below 18 years

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

4.5 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.

Those medicines that have been demonstrated to have a clinically significant impact on lamotrigine metabolism are outlined below:

Effects of other medicines on glucoronidation of lamotrigine

Medicines that significantly inhibit glucuronidation of lamotrigine	**Medicines that significantly induce glucuronidation of lamotrigine**	**Medicines that do not significantly inhibit or induce glucuronidation of lamotrigine**
Valproate	Phenytoin	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbitone	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate
	Ethinyloestradiol/ levonorgestrel combination**	Zonisamide
	Atazanavir/ritonavir*	Lithium
		Buproprion
		Olanzapine
		Aripiprazole
		Lacosamide
		Perampanel

There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Interactions involving antiepileptic medicines

Concomitant use of valproic acid increases the half-life and plasma concentrations of LAMITOR due to competition for hepatic glucuronidation. Plasma concentrations of valproic acid may decrease slightly when LAMITOR is added. The appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine leading to increased clearance and subsequent reduction of the elimination half-life of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

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

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

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

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

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

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

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

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

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

In a pooled analysis of data from three placebo-controlled studies 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.

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

Interactions involving other psychoactive medicines

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

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

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

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

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100 to 400 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for a further 7 days. An average reduction of approximately 10 % in C_{max}

and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

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

Interactions involving hormonal contraceptives

LAMITOR does not seem to affect plasma concentrations of ethinyloestradiol and levonorgestrel following the administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, any change in the menstrual bleeding pattern should be reported to the patient's physician.

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52 % and 39 % reduction in lamotrigine AUC and C_{max}, respectively. Serum lamotrigine concentrations 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. Breakthrough seizures have been reported in women using contraceptives.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

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

in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted. Cases of unplanned pregnancy, menstrual disorders and amenorrhoea have been reported. Any change in the menstrual bleeding patterns should be reported to the physician of the patient.

Interactions involving other medicines

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and C_{max} of lamotrigine (single 100 mg dose) by an average of 32 % and 6 %, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

Data from *in vitro* assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of Organic Transporter 2 (OCT 2) at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC_{50} value of 53.8 µM. Co-administration of lamotrigine with renally excreted medicines, which are substrates of OCT 2 (e.g., metformin, gabapentin and varenicline), may result in increased plasma levels of these medicines.

4.6 Fertility, pregnancy and lactation

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

Pregnancy: Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during LAMITOR therapy should be ensured.

Lactation: There is limited information on the use of LAMITOR in lactation. Preliminary data indicate that it passes into breast milk in concentrations usually of the order of 40 to 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

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. Therefore, patients should see how LAMITOR therapy affects them before driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: with in each frequency grouping, and listed in the table below.

System organ class	**Frequency**
Blood and lymphatic system disorders	
Haematological abnormalities[1] including neutropenia, Leucopenia, Eosinophilia, Anaemia, Thrombocytopenia, Pancytopenia, Aplastic anaemia, Agranulocytosis Haemophagocytic lymphohistiocytosis	Less Frequent
Lymphadenopathy[1]	Frequency not known
Immune system disorders	
Hypersensitivity syndrome[2] (Symptoms such as fever, malaise, influenza-like symptoms, drowsiness, lymphadenopathy, facial oedema and rarely, hepatic dysfunction, leucopenia and thrombocytopenia have been reported in conjunction with rashes as part of a hypersensitivity syndrome (see WARNINGS).	Less Frequent

Hypogammaglobulinaemia Disseminated intravascular coagulation. Progressive immunosuppression	Frequency not known
Psychiatric disorders	
Aggression, Irritability	Frequent
Confusion, Hallucinations, Tics, Anxiety, Depression, Amnesia	Less Frequent
Nightmares	Frequency not known
Nervous system disorders	
Headache[§] Somnolence[†§], Dizziness[†§], Drowsiness, Tremor[†], Vertigo, Paraesthesia, Nystagmus[†] Insomnia[†], Agitation[§]	Frequent

Ataxia†, Aseptic meningitis Unsteadiness, Coordination abnormalities, Worsening of Parkinson's disease[3], Extrapyramidal effects, Choreoathetosis†, Increase in seizure frequency, Dysarthria,	Less Frequent
Eye disorders	
Diplopia†, Blurred vision† Conjunctivitis	Less Frequent
Respiratory, thoracic and mediastinal disorders	
Angio-oedema	Less Frequent
Gastrointestinal disorders	
Nausea†, Vomiting†, Gastrointestinal disturbance Diarrhoea†, Dry mouth§	Frequent
Constipation, Dyspepsia	Less frequent
Oesophagitis, Pancreatitis	Frequency unknown
Hepatobiliary disorders	
Hepatic failure, Hepatic dysfunction[4], Increased liver function tests	Less Frequent
Skin and subcutaneous tissue disorders	
Skin rash[5†§] Sepsis, Abscess, Cellulitis,	Frequent

Alopecia, Photosensitivity reaction, Stevens–Johnson Syndrome§, Toxic epidermal necrolysis Drug Reaction with Eosinophilia and Systemic[2] Symptoms, Petechia, Necrotising fasciitis	Less Frequent
Musculoskeletal and connective tissue disorders	
Arthralgia§	Frequent
Lupus-like reactions	Less Frequent
Renal and urinary disorders	
Proteinuria, Urinary tract infection	Frequent
Tubulointerstitial nephritis, Tubulointerstitial nephritis and uveitis syndrome	Frequency not known
General disorders and administration site conditions	
Tiredness†, Pain§, Back pain§	Frequent
Fever, Asthenia	Less frequent
Multi-organ failure	Frequency not known

Epilepsy monotherapy (identified by†) and bipolar disorder (identified by §).

Description of selected adverse reactions

[1]Haematological abnormalities and lymphadenopathy may or may not be associated with the DRESS / hypersensitivity syndrome (see Section 4.4).

[2]Rash has also been reported as part of this syndrome, also known as DRESS. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, and abnormalities of the blood, liver and kidney. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though

rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately, and LAMITOR discontinued if an alternative aetiology cannot be established (see section 4.4).

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

There have been reports that LAMITOR may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

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

[5]In clinical trials in adults, skin rashes occurred in up to 8 to 12% of patients taking lamotrigine and in 5 to 6 % of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2 % of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of LAMITOR (see section 4.4).

Serious potentially life-threatening skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) and DRESS have been reported. Although the majority recover on withdrawal of lamotrigine treatment, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

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

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

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with lamotrigine. The mechanism by which lamotrigine affects bone metabolism has not been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms and signs

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

Treatment

In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: ATC code: N03AX09.

Mechanism of action

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 key role in the generation of epileptic seizures. These effects are likely to contribute to the anticonvulsant properties of lamotrigine.

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

The results of pharmacological studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilise neuronal membranes and inhibit neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a key role in the generation of epileptic seizures.

Clinical efficacy in the prevention of depressive episodes in patients with bipolar disorder: Two pivotal studies have demonstrated efficacy in the prevention of depressive episodes in patients with bipolar I disorder.

One was a multi-centre, double-blind, double-dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medicine, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200, 400 mg/day), lithium (serum levels of 0,8 to 1,1 mEq/ℓ) or placebo for a

maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was 'Time to Intervention for a Mood Episode (TIME)', where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0,003 to 0,029. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine patients had longer times to first depressive episode than placebo patients (p = 0,047) and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

Another study was a multi-centre, double-blind, double-dummy, placebo and lithium-controlled, randomised, flexible dose evaluation of lamotrigine in the long-term prevention of relapse and recurrence of manic and/or depression in patients with bipolar I disorder who had recently or were currently experiencing a manic or hypomanic episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medicine, patients were randomly assigned into one of three treatment groups: lamotrigine (100 to 400 mg/day), lithium (serum levels of 0,8 to 1,1 mEq/ℓ) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was 'Time to Intervention for a Mood Episode (TIME),' where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0,003 to 0,023. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine patients had longer times to first depressive episode than placebo patients (p = 0,015) and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant. In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on lamotrigine therapy was not significantly different to placebo.

5.2 Pharmacokinetic properties

Lamotrigine is rapidly and completely absorbed from the gut. The absorption is unaffected by food.

Absorption

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

Distribution

Binding to plasma proteins is about 55 %; it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0,92 to 1,22 L/kg.

Biotransformation

Lamotrigine is metabolised primarily by glucuronidation. 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 medicines metabolised by cytochrome P_{450} enzymes are unlikely to occur.

Elimination

The apparent plasma clearance in healthy subjects is approximately 30 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10 % is excreted unchanged in the urine. Only about 2 % of lamotrigine-related material is excreted in faeces. Clearance and half-life are independent of dose. The apparent plasma half-life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32 % compared with normal controls but the values are within the range for the general population.

The half-life of lamotrigine is greatly affected by concomitant medicines. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing medicines such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see section 4.2).

Linearity

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

Special population

Children

Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing medicines such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (see section 4.2).

Infants aged 2 to 26 months

In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co- administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47 %). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher C_{max} levels are likely to be observed in some children with a body weight below 10 kg.

Elderly

Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12 % from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10 % from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0,39 mL/min/kg) lies within the range of the mean clearance values (0,31 to 0,65 mL/min/kg) obtained in nine studies with non-elderly adults after single doses of 30 to 450 mg.

Renal impairment

Twelve volunteers with chronic renal failure, and another six individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0,42 mL/min/kg (chronic renal failure), 0,33 mL/min/kg (between hemodialysis) and 1,57 mL/min/kg (during hemodialysis), compared with 0,58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42,9 hours (chronic renal failure), 57,4 hours (between

hemodialysis) and 13,0 hours (during hemodialysis), compared with 26,2 hours in healthy volunteers. On average, approximately 20 % (range = 5,6 to 35,1) of the amount of lamotrigine present in the body was eliminated during a 4 hour hemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant medicines; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

Hepatic impairment

A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0,31, 0,24 or 0,10 mL/min/kg in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared with 0,34 mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline

Ferric oxide yellow

Lactose monohydrate

Magnesium stearate

Polyvinyl pyrrolidone

Purified talc

Purified water

Silica colloidal anhydrous

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 ºC in a dry place.

Keep tablets in the original blister packs until a dose is to be taken.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

LAMITOR 25: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton.

LAMITOR 50: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton.

LAMITOR 100: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton.

LAMITOR 200: 60 tablets, as six PVC/Aluminium foil blister strips of 10 tablets each, in a carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

LAMITOR 25: 37/2.5/0051

LAMITOR 50: 37/2.5/0052

LAMITOR 100: 37/2.5/0053

LAMITOR 200: 41/2.5/0375

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

December 2008

10. DATE OF REVISION OF TEXT

22 February 2022