For the use only of Neurologists

LAMICTAL XR 25/50/100/200 mg

1. GENERIC NAME

Lamotrigine Sustained Release Tablets IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMICTAL XR 25 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 25 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 50 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 50 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 100 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 100 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow & Red), Iron Oxide Black

LAMICTAL XR 200 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 200 mg
Colours:
Titanium Dioxide IP, Indigo Carmine, Iron Oxide Black

3. DOSAGE FORM AND STRENGTH

Lamotrigine sustained release [extended release (XR)] tablets are round, biconvex, film-coated tablets. Each tablet has a white to off-white aperture present in the enteric coat on both tablet faces.
25 mg XR tablets: yellow tablets, marked '*LAMICTAL XR* 25'.
50 mg XR tablets: green tablets, marked '*LAMICTAL XR* 50'.
100 mg XR tablets: orange tablets, marked '*LAMICTAL XR* 100'.
200 mg XR tablets: blue tablets, marked '*LAMICTAL XR* 200'.

LAMICTAL XR 25 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 25 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 50 mg:

Each sustained release film-coated tablet contains:
Lamotrigine IP 50 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 100 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 100 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow & Red), Iron Oxide Black

LAMICTAL XR 200 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 200 mg
Colours:
Titanium Dioxide IP, Indigo Carmine, Iron Oxide Black

4. CLINICAL PARTICULARS

4.1.Therapeutic Indications

- ***Adults and Children (aged 13 years and over)***

LAMICTAL XR is indicated for add on therapy for partial and secondary generalised tonic-clonic seizures.

4.2 Posology and Method of Administration

LAMICTAL XR tablets should be swallowed whole, and should not be chewed, crushed or divided.

If a calculated dose of lamotrigine (e.g. for use in patients with hepatic impairment) cannot be divided into multiple lower strength *LAMICTAL XR* tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

Restarting Therapy

Prescribers should assess the need for escalation to maintenance dose when restarting *LAMICTAL XR* in patients who have discontinued lamotrigine for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine *(see 4.4 Special Warnings and Precautions for Use)*. 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 *LAMICTAL XR* exceeds five half-lives *(see 5.3 Pharmacokinetic Properties)*, *LAMICTAL XR* should generally be escalated to the maintenance dose according to the appropriate schedule.

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

When concomitant anti-epileptic drugs (AEDs) are withdrawn or other AEDs are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (*see 4.5 Drug Interactions*).

Adults and Children (aged 13 years and over)

Table 1: Recommended treatment regimen for adults and children aged 13 years and over

<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 concomitant medications</td><td>12.5 mg
(given 25 mg alternate days)</td><td>25 mg
(once a day)</td><td>150 – 250 mg
(once a day)
To achieve maintenance, doses may be increased by 50 mg every week</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 4.5 Drug Interactions)</td><td>50 mg
(once a day)</td><td>100 mg
(once a day)</td><td>400 – 600 mg
(once a day)
To achieve maintenance, doses may be increased by 100 mg every week</td></tr>
<tr><td>This dosage regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see 4.5 Drug Interactions)</td><td>25 mg
(once a day)</td><td>50 mg
(once a day)</td><td>200 – 400 mg
(once a day)
To achieve maintenance, doses may be increased by 50 mg every week</td></tr>
<tr><td colspan="5">In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see 4.5 Drug Interactions), the treatment regimen as recommended for LAMICTAL XR with concurrent valproate should be used.</td></tr>
</table>

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see *4.4 Special Warnings and Precautions for Use*).

Conversion from LAMICTAL immediate release tablets or dispersible/chewable tablets to LAMICTAL XR tablets

Patients may be converted directly from *LAMICTAL* immediate release (IR) tablets or dispersible / chewable tablets to *LAMICTAL XR* tablets (*see 5.3 Pharmacokinetic Properties*). The initial dose of *LAMICTAL XR* should match the total daily dose of *LAMICTAL* IR. Following conversion to *LAMICTAL XR*, the dose may be adjusted depending on therapeutic response.

- ***Children aged 12 years and under***

LAMICTAL XR tablets have not been studied in children aged twelve years and under (*see 4.4 Special Warnings and Precautions for Use*).

GENERAL DOSING RECOMMENDATIONS FOR *LAMICTAL XR* IN SPECIAL PATIENT POPULATIONS

- ***Women taking hormonal contraceptives***

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

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (*see 4.4 Special Warnings and Precautions for Use* and *4.5 Drug Interactions*), no adjustments to the recommended dose escalation guidelines for *LAMICTAL XR* should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether *LAMICTAL XR* is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether *LAMICTAL XR* is added in the absence of valproate or an inducer of lamotrigine glucuronidation (see Table 1).

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

The maintenance dose of *LAMICTAL XR* will in most cases need to be increased by as much as two-fold (*see 4.4 Special Warnings and Precautions for Use* and *4.5 Drug Interactions*). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases.

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

The maintenance dose of *LAMICTAL XR* will in most cases need to be decreased by as much as 50% (*see 4.4 Special Warnings and Precautions for Use* and *4.5 Drug Interactions*). It is recommended to gradually decrease the daily dose of lamotrigine by 50 to 100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise.

- ***Use with atazanavir/ritonavir***

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

In patients already taking maintenance doses of *LAMICTAL XR* and not taking glucuronidation inducers, the *LAMICTAL XR* 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 recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population.

- ***Hepatic impairment***

Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (*see 5.3 Pharmacokinetic Properties*).

- ***Renal impairment***

Caution should be exercised when administering *LAMICTAL XR* to patients with renal failure. For patients with end-stage renal failure, initial doses of *LAMICTAL XR* should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (*see 4.4 Special Warnings and Precautions for Use*). For more detailed pharmacokinetic information (*see 5.3 Pharmacokinetic Properties*).

4.3 Contraindications

LAMICTAL XR tablets are contraindicated in individuals with known hypersensitivity to lamotrigine, or any other ingredient of the preparation.

4.4 Special Warnings and Precautions for Use

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (*see 4.8 Undesirable Effects*).

In adults enrolled in studies utilising the current lamotrigine IR dosing recommendations, the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as SJS (1 in 1000).

The risk of serious skin rashes in children is higher than in adults. *LAMICTAL XR* tablets have not been studied in children aged 12 years and under, and are therefore not recommended for use in this population.

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

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

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

All patients who develop a rash should be promptly evaluated and *LAMICTAL XR* withdrawn immediately unless the rash is clearly not drug related. It is recommended that *LAMICTAL XR* not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney and aseptic meningitis (*see 4.8 Undesirable Effects*). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and *LAMICTAL XR* discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has occurred in patients taking *LAMICTAL* (*see 4.8 Undesirable Effects*). HLH is a syndrome of pathological immune activation, which can be life threatening, characterized by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy; cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation.

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

Suicide risk

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

Twenty-five to 50% of patients with bipolar disorder attempt suicide at least once, and may experience worsening of their depressive symptoms and/or the emergence of suicidal

ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including lamotrigine.

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEDs (including lamotrigine) has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.

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

Hormonal contraceptives

Effects of hormonal contraceptives on *LAMICTAL XR* efficacy:

An ethinylestradiol/levonorgestrel (30 micrograms/150 micrograms) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (*see 4.5 Drug Interactions*). Following titration, higher maintenance doses of *LAMICTAL XR* (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when *LAMICTAL XR* dose increases are made in the days before or during the week of inactive medication. For dosing instructions *see 4.6 Use in Special Populations*.

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

Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of *LAMICTAL XR* on hormonal contraceptive efficacy:

An interaction study in 16 healthy volunteers has shown that when lamotrigine IR 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 4.5 Drug Interactions*). 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 *LAMICTAL XR* cannot be excluded. Therefore patients taking *LAMICTAL XR* should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

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

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (*see 4.5 Drug Interactions*). This may result in increased plasma levels of certain drugs that are

substantially excreted via this route. Co-administration of *LAMICTAL XR* with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

Dihydrofolate reductase

Lamotrigine is a weak inhibitor of dihydrofolate reductase, hence there is a possibility of interference with folate metabolism during long-term therapy. However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal Failure

In 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

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

Brugada-type ECG

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

Epilepsy

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

There are reports in the literature that severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of lamotrigine.

4.5 Drug Interactions

Uridine 5’-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce is own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Those drugs that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in Table 2. Specific dosing guidance for these drugs is provided in Posology and Method of Administration. In addition, this table lists those drugs which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such drugs would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Table 2: Effects of drugs on the concentration of lamotrigine

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

For dosing guidance, *see 4.2 Posology and Method of Administration — General Dosing Recommendations for LAMICTAL XR in Special Patient Populations*, plus for women taking hormonal contraceptives also see *4.4 Special Warnings and Precautions for Use*- Hormonal Contraceptives.

- ***Interactions involving AEDs (see 4.2 Posology and Method of Administration)***

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine.

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

In a study in healthy adult volunteers using doses of 200 mg lamotrigine IR and 1200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine.

In a study of healthy volunteers, co-administration of felbamate (1200 mg twice daily) with lamotrigine IR (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 IR both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential drug 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 IR resulted in a 15% increase in topiramate concentrations.

In a study of patients with epilepsy, co-administration of zonisamide (200 to 400 mg/day) with lamotrigine IR (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 clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10%.

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

- ***Interactions involving other psychoactive agents (see 4.2 Posology and Method of Administration)***

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 IR.

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. Lamotrigine IR at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of lamotrigine IR 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 IR 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 C_{max} 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 microsome suggested that lamotrigine does not reduce the clearance of drugs 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 lamotrigine pharmacokinetics

In a study of 16 female volunteers, 30 micrograms ethinylestradiol/150 micrograms 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 - *see 4.2 Posology and Method of Administration - General Dosing Recommendations for LAMICTAL XR in Special Patient Populations* (for dosing instructions for women taking hormonal contraceptives) and *4.4 Special Warnings and Precautions for Use – Hormonal Contraceptives*.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine IR had 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 was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum FSH, LH and estradiol 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 4.4 Special Warnings and Precautions for Use*). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

- ***Interactions involving other medications***

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 treatment regimen recommended for *LAMICTAL XR* and concurrent glucuronidation inducers should be used (*see 4.2 Posology and Method of Administration*).

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 treatment regimen recommended for *LAMICTAL XR* and concurrent glucuronidation inducers should be used (*see 4.2 Posology and Method of Administration*).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively (*see 4.2 Posology and Method of Administration - General Dosing Recommendations for LAMICTAL XR in Special Patient Populations*).

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

Data from *in vitro* assessment of the effect of lamotrigine at OCT 2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC_{50} value of 53.8 µM (*see 4.4 Special Warnings and Precautions for Use*).

- ***Interactions involving laboratory tests***

LAMICTAL 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 Use in Special Populations

Fertility

Administration of lamotrigine did not impair fertility in animal reproductive studies.

There is no experience of the effect of lamotrigine on human fertility.

Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 8,700 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations. Although data from a limited number of registries have reported an increase in the risk of isolated oral cleft malformations, a completed case control study did not demonstrate an increased risk of oral clefts compared to other major congenital malformations following exposure to lamotrigine (*see 6. Non-Clinical Studies*).

The data on use of lamotrigine in polytherapy combinations are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant lamotrigine use.

As with other medicines, *LAMICTAL XR* should only be used during pregnancy if the expected benefits outweigh the potential risks.

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 *LAMICTAL XR* therapy should be ensured.

Lactation

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mothers. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

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

Elderly (over 65 years of age)

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

Hepatic impairment

Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (*see 5.3 Pharmacokinetic Properties*).

Renal impairment

Caution should be exercised when administering *LAMICTAL XR* to patients with renal failure. For patients with end-stage renal failure, initial doses of *LAMICTAL XR* should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (*see 4.4 Special Warnings and Precautions for Use*). For more detailed pharmacokinetic information (*see 5.3 Pharmacokinetic Properties*).

4.7 Effects on Ability to Drive and Use Machines

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine IR, adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how *LAMICTAL XR* therapy affects them before driving or operating machinery.

As there is individual variation in response to all anti-epileptic drug therapy, patients should consult their physician on the specific issues of driving and epilepsy.

4.8 Undesirable Effects

The adverse reactions identified from epilepsy or bipolar disorder (an indication of *LAMICTAL IR)* clinical trials data have been divided into indication specific sections. Additional adverse reactions identified through post-marketing surveillance for both indications are included in the post-marketing section. All three sections should be consulted when considering the overall safety profile of *LAMICTAL*.

The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to < 1/100); rare (≥1/10,000 to < 1/1000); very rare (< 1/10,000).

EPILEPSY

The following adverse reactions were identified during epilepsy clinical trials and should be considered alongside those seen in the bipolar disorder clinical trials and post-marketing sections for an overall safety profile of *LAMICTAL.*

Skin and subcutaneous tissue disorders

Very common:	Skin rash
Rare:	Stevens-Johnson syndrome
Very rare:	Toxic epidermal necrolysis

In double-blind, add-on clinical trials in adults, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% 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 lamotrigine (*see 4.4 Special Warnings and Precautions for Use*).

Rarely, serious potentially life threatening skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (*see 4.4 Special Warnings and Precautions for Use*).

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 4.2 Posology and Method of Administration*)

- concomitant use of valproate (*see 4.2 Posology and Method of Administration*).

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms (*see 4.4 Special Warnings and Precautions for Use Immune system disorders***).

Blood and lymphatic system disorders

Very rare: Haematological abnormalities (including, neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis), lymphadenopathy.

Haematological abnormalities and lymphadenopathy may or may not be associated with DRESS/Hypersensitivity Syndrome (*see 4.4 Special Warnings and Precautions for Use and Immune system disorders***).

Immune system disorders

Very rare: DRESS/Hypersensitivity syndrome** including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney.

**Rash has also been reported as part of this syndrome which shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately, and *LAMICTAL XR* discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common: Aggression, irritability
Very rare: Tics, hallucinations, confusion

Nervous system disorders

Very common: Headache
Common: Somnolence, insomnia, dizziness, tremor
Uncommon: Ataxia
Rare: Nystagmus

Eye disorders

Uncommon: Diplopia, blurred vision.

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea.

Hepatobiliary disorders

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

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

Musculoskeletal and connective tissue disorders

Very rare: Lupus-like reactions.

General disorders and administration site conditions

Common: Tiredness.

BIPOLAR DISORDER

The following adverse reactions were identified during bipolar disorder clinical trials and should be considered alongside those seen in the epilepsy clinical trials and post--marketing sections for an overall safety profile of *LAMICTAL*.

Skin and subcutaneous tissue disorders

Very Common: Skin rash
Rare: Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Nervous system disorders

Very Common: Headache
Common: Agitation, somnolence, dizziness

Musculoskeletal and connective tissue disorders

Common: Arthralgia

General disorders and administration site conditions

Common: Pain, back pain

POST-MARKETING:

This section includes adverse reactions identified through post-marketing surveillance for both indications. These adverse reactions should be considered alongside those seen in the epilepsy and bipolar disorder clinical trials sections for an overall safety profile of *LAMICTAL*.

Blood and lymphatic system disorders

Very rare: Haemophagocytic lymphohistiocytosis *(see 4.4 Special Warnings and Precautions for Use)*

Skin and subcutaneous tissue disorders

Rare: Alopecia

Psychiatric disorders

Very rare: Nightmares

Nervous system disorders

Very common:	Somnolence, ataxia, headache, dizziness
Common:	Nystagmus, tremor, insomnia
Rare:	Aseptic meningitis (*see 4.4 Special Warnings and Precautions for Use)*
Very rare:	Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis

There have been reports that *LAMICTAL* 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.

Eye disorders

Very common:	Diplopia**,** blurred vision
Rare:	Conjunctivitis

Gastrointestinal disorders

Very common:	Nausea**,** vomiting
Common:	Diarrhoea

Renal and Urinary disorders

Very rare:	Tubulointerstitial nephritis*

*may occur in association with uveitis

Epilepsy only

Nervous system disorders

Very rare: Increase in seizure frequency

4.9 Overdose

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose of lamotrigine IR, have 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.

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

ATC Code: N 03 AX 09

5.1 Mechanism of Action

The results of pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage-gated sodium channels. It produces a use- and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

5.2 Pharmacodynamic Effects

In tests designed to evaluate the central nervous system effects of drugs, the results obtained using doses of 240 mg lamotrigine IR administered to healthy volunteers did not differ from placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor co-ordination and eye movements, increased body sway and produced subjective sedative effects.

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

5.3 Pharmacokinetic Properties

Absorption

The dissolution rate of lamotrigine from the XR tablet is controlled over a period of approximately 12-15 hours.

In healthy volunteers not receiving any other medications and given lamotrigine XR once daily, the systemic exposure to lamotrigine increased in direct proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and 50 mg, the increase was less than dose-proportional, with a 2–fold increase in dose resulting in an approximately 1.6–fold increase in systemic exposure.

In an open-label crossover study of 44 subjects with epilepsy receiving concomitant AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration of equivalent total doses of lamotrigine XR given once daily with those of lamotrigine IR given twice daily. In this study, the median time to peak concentration (T_{max}) following administration of lamotrigine XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone, 9 to 11 hours in patients taking valproate, and 6 to

10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate.

The steady-state trough concentrations for lamotrigine XR were equivalent to, or higher than those of lamotrigine IR, depending on concomitant AED (see Table **3**). A reduction in the lamotrigine peak serum concentration (C_{max}) was observed for lamotrigine XR compared to lamotrigine IR, resulting in a decrease in the peak to trough fluctuation in serum lamotrigine concentrations. The degree of fluctuation was reduced by 17% in patients taking AEDs that induce lamotrigine glucuronidation, 34% in patients taking valproate and 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate. Lamotrigine XR and lamotrigine IR regimens were equivalent with respect to area under the curve (AUC) for patients receiving AEDs other than those known to induce lamotrigine glucuronidation. The relative bioavailability of lamotrigine XR was approximately 21% lower than lamotrigine IR in subjects receiving enzyme-inducing AEDs.

Table 3:
Steady-state bioavailability of lamotrigine XR relative to lamotrigine IR at equivalent daily doses (ratio of XR to IR 90% confidence interval, CI)[#]

Concomitant AED	**AUC ($_{0\text{-}24ss}$)**	**C_{max}**	**C_{min}**
AEDs that significantly induce glucuronidation of lamotrigine (*see 4.5 Drug Interactions*)	0.79 (0.69,0.90)	0.71 (0.61,0.82)	0.99 (0.89,1.09)
Valproate	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
AEDs other than the above	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

[#] bioequivalence was concluded if the CI was within the range 0.8 to 1.25

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.

Metabolism

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

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and drugs metabolised by cytochrome P_{450} enzymes are unlikely to occur.

Elimination

Elimination data were generated using the lamotrigine IR formulation. The mean steady state clearance in healthy adults is 39 ± 14 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 drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 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 medication. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (*see 4.2 Posology and Method of Administration* and *Interaction with Other Medicaments and Other Forms of Interaction*).

Since the half-life of lamotrigine following administration of single doses of lamotrigine IR is comparable to that observed following administration of lamotrigine XR, similar changes in the half-life of lamotrigine would be expected for lamotrigine XR.

Special Patient Populations

- **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 of lamotrigine IR, 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 of lamotrigine IR. 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 doses of 30 to 450 mg.

- **Patients with renal impairment**

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine IR. Mean CL/F were 0.42 mL/min/kg (chronic renal failure), 0.33 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 = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4 hours haemodialysis session. For this patient population, initial doses of *LAMICTAL XR* should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment.

- **Patients with hepatic impairment**

A single-dose pharmacokinetic study with lamotrigine IR 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 to 0.34 mL/min/kg in the healthy controls. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

5.4 Clinical Studies

Clinical efficacy of adjunctive LAMICTAL XR therapy in partial seizures

The effectiveness of *LAMICTAL XR* as adjunctive therapy in patients with partial seizures was established in a 19–week multi-centre, double-blind, placebo-controlled trial (LAM100034) in 236 patients aged 13 years and over. Patients with at least 8 partial seizures during an 8-week baseline phase were randomised to treatment with *LAMICTAL XR* or placebo added to their current regimen of one or two AEDs. Approximately half of the patients were taking two concomitant AEDs at baseline. Target doses for *LAMICTAL XR* ranged from 250 mg/day to 500 mg/day based on concomitant AED treatment.

The primary endpoint was the percent change from baseline in partial seizure frequency during the entire double-blind treatment phase. For the intent-to-treat population, the median percent reduction in partial seizures was 46% in patients treated with *LAMICTAL XR* and 24% on placebo, a difference that was statistically significant (p=0.0004).

For the intent-to-treat population, the percentage of subjects who showed a $\geq$50% reduction in partial seizure frequency over the entire double-blind treatment phase was significantly greater in the group treated with *LAMICTAL XR* (42%) compared with placebo (24%) (p = 0.0037). Among these patients, the time (in weeks) to achieve and maintain a $\geq$50% reduction in partial seizure frequency was significantly shorter for the group treated with *LAMICTAL XR* compared with placebo (p = 0.0007). Statistical significance was evident at Day 18 (p = 0.04).

Clinical efficacy of adjunctive LAMICTAL XR therapy in primary generalised tonic-clonic (PGTC) seizures

The effectiveness of *LAMICTAL XR* as adjunctive therapy was established in PGTC seizures in a 19-week, multi-centre, double-blind, randomised, placebo-controlled study (LAM100036) in 143 patients 13 years of age and older. Patients with at least three PGTC seizures during an 8-week baseline phase were randomised to treatment with *LAMICTAL XR* or placebo added to their current regimen of one or two AEDs. Approximately 40% of the patients were taking two concomitant AEDs at baseline. Patients were dosed on a fixed-dose regimen, with target doses ranging from 200 mg/day to 500 mg/day of *LAMICTAL XR* based on concomitant AED(s).

The primary efficacy endpoint was percent change from baseline in PGTC seizure frequency during the double-blind treatment phase. For the intent-to-treat population, the median percent reduction in PGTC seizure frequency was 75% in patients treated with

LAMICTAL XR and 32% in patients treated with placebo, a difference that was statistically significant ($p<0.0001$).

For the intent-to-treat population, the percentage of subjects who showed a ≥50% reduction in PGTC seizure frequency over the entire double-blind treatment phase was significantly greater in the group treated with *LAMICTAL XR* (70%) compared with placebo (32%; $p<0.0001$); statistical significance was evident at Day 8 ($p<0.05$).

6 NONCLINICAL STUDIES

6.1 Animal Toxicology and Pharmacology

Reproductive toxicology studies with lamotrigine in animals at doses less than the human dose of 400 mg/day [on a body surface area (mg/m^2) basis] showed developmental toxicity (increased mortality, decreased body weight, increased structural variations, neurobehavioral abnormalities), but no teratogenic effects. However, as lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

The results of a wide range of mutagenicity tests indicate that lamotrigine does not present a genetic risk to man.

Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

7 DESCRIPTION

Lamotrigine sustained release [(XR)] tablets are round, biconvex, film-coated tablets. Each tablet has a white to off-white aperture present in the enteric coat on both tablet faces.
25 mg XR tablets: yellow tablets, marked '*LAMICTAL XR* 25'.
50 mg XR tablets: green tablets, marked '*LAMICTAL XR* 50'.
100 mg XR tablets: orange tablets, marked '*LAMICTAL XR* 100'.
200 mg XR tablets: blue tablets, marked '*LAMICTAL XR* 200'.

LAMICTAL XR 25 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 25 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 50 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 50 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow), Iron Oxide Black

LAMICTAL XR 100 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 100 mg
Colours:
Titanium Dioxide IP, Ferric Oxide USPNF (Yellow & Red), Iron Oxide Black

LAMICTAL XR 200 mg:
Each sustained release film-coated tablet contains:
Lamotrigine IP 200 mg
Colours:
Titanium Dioxide IP, Indigo Carmine, Iron Oxide Black

See 8. Pharmaceutical Particulars for list of excipients.

8 PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core, 25 and 50 mg XR tablets:

Lactose monohydrate
Hypromellose
Silicon dioxide
Magnesium stearate.

***Tablet core, 100 mg and 200 mg XR tablets*:**

Lactose monohydrate
Hypromellose
Magnesium stearate.

Coloured sub-coat:

25 mg XR tablets - Opadry Yellow (*HPMC 2910/Hypromellose 6cP; Titanium Dioxide; Iron Oxide Yellow (Ferric Oxide USPNF Yellow); Macrogol/ PEG400*).

50 mg XR tablets - Opadry Green (*HPMC 2910/Hypromellose 6cP; Titanium Dioxide; Iron Oxide Yellow (Ferric Oxide USPNF Yellow); Iron Oxide Black*).

100 mg XR tablets - Opadry Orange [*HPMC 2910/Hypromellose 6cP; Titanium Dioxide; Iron Oxide Yellow (Ferric Oxide USPNF Yellow); Macrogol/ PEG400; Iron Oxide Red (Ferric Oxide USPNF Red*)].

200 mg XR tablets - Opadry Blue (*HPMC 2910/Hypromellose 6cP; Titanium Dioxide; Macrogol/ PEG400; FD&C Blue #2/ Indigo Carmine Aluminium Lake*).

Enteric coat:

Methacrylic acid copolymer dispersion Type C
Triethyl citrate
Glycerol monostearate
Polysorbate 80.

Printing Ink (Opacode S-1-17823 or S-1-17822 or S-1-17843):

Opacode S-1-17823: *[Shellac Glaze-45% (20% Esterified) in Ethanol; Isopropyl Alcohol; Iron Oxide Black; N-Butyl Alcohol; Propylene Glycol; Ammonium Hydroxide 28%].*

Opacode S-1-17822: *[Shellac Glaze ~ 45% (20% Esterified) in Ethanol; Iron Oxide Black; N-Butyl Alcohol; Isopropyl Alcohol; Propylene Glycol; Ammonium Hydroxide 28%]*.

Opacode S-1-17843: *[Shellac Glaze ~ 45% (20% Esterified) in Ethanol; Iron Oxide Black; N-Butyl Alcohol; Isopropyl Alcohol; Propylene Glycol; Ammonium Hydroxide 28%]*.

8.1 Incompatibilities

No incompatabilities have been identified.

8.2 Shelf-Life

LAMICTAL XR 25 mg:

- 18 months (Blister)
- 24 months (HDPE Bottle)

LAMICTAL XR 50/100/200 mg: 36 months (Blister and HDPE Bottle)

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

LAMICTAL XR Extended Release Tablets may be packaged in HDPE bottles or blister packs (30 tablets per bottle/blister pack).

Bottles:
Tablets are packed with desiccant into opaque, white HDPE bottles with polypropylene child resistant or continuous thread closures, with a polyethylene faced induction heat seal liner. The HDPE is pigmented white with titanium dioxide.

Blister Strips:
Tablets are packed into blister strips. The blister strip comprises a PVC/PVdC film sealed with a push through aluminium lidding foil.

All presentations may not be marketed in India.

8.4 Storage and Handling Information

Store at temperature not exceeding 30°C, protected from light.

Keep out of reach of children.

9 PATIENT COUNSELLING INFORMATION

Registered medical practitioners may counsel their patients (and/or their patient's parents) about the special warnings and precautions for use, drug intercations, undesirable effects, and any relevant contraindications of *LAMICTAL XR*. Patients (and/or their patient's parents) may also be informed about posology, method of administration and storage/handling information as applicable.

10 DETAILS OF MANUFACTURER

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11 DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Import-166/2012 dated 6th August 2012

12 DATE OF REVISION

29-Jul-2020

Version: *LAM-XR/PI/IN/2020/02*

Adapted from Lamictal XR GDS 48/ IPI 19 dated 18 February 2020.