For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

LAMITOR DT

1. Generic Name

Lamotrigine Dispersible Tablets I.P.

2. Qualitative and quantitative composition

LAMITOR DT-25

Each uncoated dispersible tablet contains:

Lamotrigine I.P……..25 mg

In a flavoured base

The excipients used are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

LAMITOR DT-50

Each uncoated dispersible tablet contains:

Lamotrigine I.P……..50 mg

In a flavoured base

The excipients used are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

LAMITOR DT-100

Each uncoated dispersible tablet contains:

Lamotrigine I.P……100 mg

In a flavoured base

The excipients used are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

3. Dosage form and strength

Dosage Form: Uncoated dispersible Tablets

Strength: 25mg, 50mg and 100mg

4. Clinical particulars

4.1 Therapeutic indication

Lamotrigine tablets are indicated as add on therapy of partial and secondary generalised tonic clonic seizures.

4.2 Posology and method of administration

Lamitor DT should not be chewed or crushed.

Direction for use: Disperse the tablet in 10ml of boiled and cooled water before administration.
Restarting therapy

Prescribers should assess the need for escalation to maintenance dose when restarting

Lamitor DT in patients who have discontinued Lamitor DT for any reason, since the risk

of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see section *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 lamotrigine exceeds five half-lives (see section *Pharmacokinetic properties*), Lamitor DT should generally be escalated to the maintenance dose according to the appropriate schedule.

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

Epilepsy

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above and for children and adolescents aged 2 to 12 years are given below. Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section *Special warnings and precautions for use*).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimens containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section *Drugs interactions*).

Adults and adolescents aged 13 years and above – recommended treatment regimen in epilepsy

Treatment regimen	**Weeks 1 + 2**	**Weeks 3 + 4**	**Usual maintenance dose**
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section *Drugs interactions*)**:**			
This dosage regimen should be used with valproate regardless of any concomitant medicinal products	12.5 mg/day (given as 25mg on alternate days)	25 mg/day (once a day)	100 - 200 mg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 25 - 50 mg every one to two weeks until optimal response is achieved
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section *Drugs interactions*)**:**			

This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	50 mg/day (once a day)	100 mg/day (two divided doses)	200 - 400 mg/day (two divided doses) To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved 700 mg/day has been required by some patients to achieve desired response
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section *Drugs interactions*)**:**			
This dosage regimen should be used with other	25 mg/day (once a day)	50 mg/day (once a day)	100 - 200 mg/day (once a day or two divided doses)
medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation			To achieve maintenance, doses may be increased by maximum of 50 100 mg every one to two weeks until optimal response is achieved
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section *Drugs interactions*), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

Children and adolescents aged 2 to 12 years - recommended treatment regimen in epilepsy (total daily dose in mg/kg body weight/day)

Treatment regimen	**Weeks 1 + 2**	**Weeks 3 + 4**	**Usual maintenance dose**
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section *Drugs interactions*)**:**			
This dosage regimen should be used with valproate regardless of any other concomitant medicinal products	0.15 mg/kg/day* (once a day)	0.3 mg/kg/day (once a day)	1 - 5 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day

Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section *Drugs interactions*)**:**			
This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	0.6 mg/kg/day (two divided doses)	1.2 mg/kg/day (two divided doses)	5 - 15 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section *Drugs interactions*)**:**			
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1 - 10 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum of maintenance dose of 200 mg/day
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section *Drugs interactions*), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			
* If the calculated daily dose in patients taking valproate is 1 mg or more but less than 2 mg, then Lamitor DT 2 mg chewable/dispersible tablets may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then Lamitor DT should not be administered.			

To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.

If epileptic control is achieved with adjunctive treatment, concomitant AEDs may be withdrawn and patients continued on Lamitor DT monotherapy.

Children below 2 years

There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section *Special warnings and precautions for use*). There are no data in children below 1 month of age. Thus Lamitor DT is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections *Special warnings and precautions for use*, *Pharmacodynamic properties* and *Pharmacokinetic properties*.

General dosing recommendations for Lamitor DT in special patient populations

Women taking hormonal contraceptives

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. Following titration, higher maintenance doses of lamotrigine (by as much as twofold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections *Special warnings and precautions for use* and *Drugs interactions*).

Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation

The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections *Special warnings and precautions for use* and *Drugs 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. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. 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; see sections *Special warnings and precautions for use* and *Drugs interactions*).

Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation

The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections *Special warnings and precautions for use* and *Drugs interactions*). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

Starting lamotrigine in patients already taking hormonal contraceptives

Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation

Adjustment to the recommended maintenance dose of lamotrigine may not be required.

Use with atazanavir/ritonavir

No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing atazanavir/ritonavir therapy.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section *Drugs interactions*).

Use with lopinavir/ritonavir

No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing lopinavir/ritonavir therapy.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section *Drugs interactions*).

Elderly (above 65 years)

No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a nonelderly adult population (see section *Pharmacokinetic properties*).

Renal impairment

Caution should be exercised when administering Lamitor DT to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections *Special warnings and precautions for use* and *Pharmacokinetic properties*).

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 section *Pharmacokinetic properties*).

4.3 Contraindications

Hypersensitivity to active substances or to any of the excipients of this product.

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), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (HSS) (see section *Undesirable effects*).

In adults enrolled in studies utilizing the current lamotrigine dosing recommendations the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as Stevens–Johnson syndrome (1 in 1000). In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000.

The risk of serious skin rashes in children is higher than in adults. Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in children is from 1 in 300 to 1 in 100.

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

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

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

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

All patients (adults and children) who develop a rash should be promptly evaluated and Lamitor DT withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that Lamitor DT not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk. If the patient has developed SJS, TEN or DRESS with the use of lamotrigine, treatment with lamotrigine must not be re-started in this patient at any time.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver and aseptic meningitis (see section *Undesirable effects*). 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 DT 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.

There have also been reports of photosensitivity reactions associated with lamotrigine use. In several cases, the reaction occurred with a high dose (400mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing

signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs 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 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 medications for bipolar disorder, including lamotrigine. Therefore patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal 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 (see section *Drugs interactions*). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pillfree week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section *Posology and method of administration*). 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 firstline 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

Reportedly, an interaction study in 16 healthy volunteers has shown that when 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 (see section *Drugs 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 lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy [see section *Use in special populations (such as pregnant women, lactating women, paediatricpatients, geriatric patients etc.)*]. 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 reported 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 DT should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

Excipient of Lamotrigine tablets

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

Lamotrigine tablets contain less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium free'.

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

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

A clinically significant worsening of seizure frequency instead of an improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Myoclonic seizures may be worsened by lamotrigine.

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

Precautions relating 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.

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.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has been reported in patients taking lamotrigine. 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.

4.5 Drugs interactions

Reportedly, interaction studies have only been performed in adults.

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.

Those drugs that have been demonstrated to have a clinically significant impact on lamotrigine metabolism are outlined here. Specific dosing guidance for these drugs is provided in Section *Posology and method of administration*.

Effects of other medicinal products on glucuronidation of lamotrigine

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

*For dosing guidance (see section *Posology and method of administration*)

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.

**Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see sections *Posology and method of administration* and *Special warnings and precautions for use*).

Interactions involving antiepileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section *Posology and method of administration*).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, pheonbarbitone or primidone, the appropriate treatment regimen should be used (see section *Posology and method of administration*).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a reported 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 reported 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 *Posology and method of administration*).

Reportedly, 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 reported 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 reported 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 reported placebo-controlled clinical trials in patients with partialonset seizures.

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

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 reported *in vitro* studies indicates that lamotrigine does not displace other AEDs from protein binding sites.

<u>Interactions involving other psychoactive agents</u>

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 reported 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 reported study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100-400 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for 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.

Reportedly, *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 medicinal products metabolised predominantly by CYP2D6.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a reported study of 16 female volunteers, dosing with 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately twofold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section *Special warnings and precautions for use*). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section *Posology and method of administration*).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a reported 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 Cmax, 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 *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 medicinal products

In a reported 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 *Posology and method of administration*).

In a reported 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 *Posology and method of administration*).

In a reported study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax 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 *Posology and method of administration*).

Data from reported *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 medicinal products, which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicinal products.

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

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Risk related to antiepileptic drugs in general

Specialist advice should be given to women who are of childbearing potential. The antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics. Risk related to lamotrigine

Pregnancy

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

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

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels. Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels during pregnancy with a potential risk of loss of seizure control. After birth lamotrigine levels may increase rapidly with a risk of dose-related adverse events. Therefore lamotrigine serum concentrations should be monitored before, during and after pregnancy, as well as shortly after birth. If necessary, the dose should be adapted to maintain the lamotrigine serum concentration at the same level as before pregnancy, or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Lactation

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

The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects, such as sedation, rash and poor weight gain.

Fertility

Animal experiments did not reveal impairment of fertility by lamotrigine (see section *Nonclinical properties*).

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all AED therapy, patients taking Lamitor DT to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.

No studies on the effects on the ability to drive and use machines have been performed. Reportedly, 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 reported clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how Lamitor DT therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects are based on available data from reported controlled clinical studies and other clinical experience and are listed below. Frequency categories are derived from controlled clinical studies. However, where no reported controlled clinical trial data are available, frequency categories have been obtained from other clinical experience.

The following convention has been utilised for the classification of undesirable effects:- Very common (≥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), not known (cannot be estimated from the available data).

System Organ Class	Adverse Event	Frequency
Blood and lymphatic system disorders	Haematological abnormalities[1] including neutropenia, leucopenia, anaemia,	Very rare
	mbocytopenia, pancytopenia, aplastic anaemia, agranulocytosis	Very rare
	Haemophagocytic lymphohistiocytosis (see section *Special warnings and precautions for use*)	
	Lymphadenopathy[1]	Not known
Immune System Disorders	Hypersensitivity syndrome[2] (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi organ failure).	Very Rare
	Hypogammaglobulinaemia	Unknown

Psychiatric Disorders	Aggression, irritability Confusion, hallucinations, tics Nightmares	Common Very rare Not known
Nervous System Disorders	Headache Somnolence, dizziness, tremor, insomnia agitation Ataxia Nystagmus Unsteadiness, movement disorders, worsening of Parkinson's disease [3], extrapyramidal effects, choreoathetosis, increase in seizure frequency Aseptic meningitis (see section *Special warnings and precautions for use*)	Very Common Common Uncommon Rare Very Rare Rare
Eye disorders	Diplopia, blurred vision Conjunctivitis	Uncommon Rare
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dry mouth	Common
Hepatobiliary disorders	Hepatic failure, hepatic dysfunction[4], increased liver function tests	Very rare
Skin and subcutaneous tissue disorders	Skin rash[5] Alopecia, photosensitivity reaction Stevens–Johnson Syndrome Toxic epidermal necrolysis Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS)	Very common Uncommon Rare Very rare Very rare
Musculoskeletal and connective tissue disorders	Arthralgia Lupus-like reactions	Common Very rare
General disorders and administration site conditions	Tiredness, pain, back pain	Common

Description of selected adverse reactions

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

[2] Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If

such signs and symptoms are present, the patient should be evaluated immediately and Lamitor DT discontinued if an alternative aetiology cannot be established.

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

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

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

[5] In reported clinical trials in adults, skin rashes occurred in up to 8-12% of patients taking lamotrigine and in 5-6% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamitor DT (see section *Special warnings and precautions for use*).

Serious potentially life-threatening skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) and drug reaction with eosinophilia and systemic symptoms (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 *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 section *Posology and method of administration*).
- concomitant use of valproate (see section *Posology and method of administration*).

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

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 side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported, including fatal cases. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has also been observed in overdose patients. Broadening of QRS duration to more than 100 msec may be associated with more severe toxicity.

Treatment

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

treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section *Pharmacokinetic properties*).

5 Pharmacological properties

5.1 Mechanism of Action

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

5.2 Pharmacodynamic properties

As per reported data, in tests designed to evaluate the central nervous system effects of medicinal products, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from placebo, whereas both 1000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, increased body sway and produced subjective sedative effects.

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

Clinical efficacy and safety in children aged 1 to 24 months

Reportedly, the efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets were the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase (for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant:

26.3%, CI95% -2.6% <> 50.2%, p=0.07.

A total of 256 subjects between 1 to 24 months of age had been exposed to lamotrigine in the dose range 1 to 15 mg/kg/day for up to 72 weeks. The safety profile of lamotrigine in children aged 1 month to 2 years was similar to that in older children except that clinically significant worsening of seizures (>=50%) was reported more often in children under 2 years of age (26%) as compared to older children (14%).

Clinical efficacy and safety in Lennox-Gastaut syndrome

There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

Study of the effect of lamotrigine on cardiac conduction

A study in healthy adult volunteers evaluated the effect of repeat doses of lamotrigine (up to 400 mg/day) on cardiac conduction, as assessed by 12-lead ECG. There was no clinically significant effect of lamotrigine on QT interval compared to placebo.

5.3 Pharmacokinetic properties

Absorption

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

Distribution

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

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

Biotransformation

UDP-glucuronyl 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 medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination

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

The half-life of lamotrigine is greatly affected by concomitant medicinal products. Mean half-life is reduced to approximately 14 hours when given with glucuronidationinducing medicinal products such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see section *Posology and method of administration*).

Linearity/non-linearity

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

Special populations

Children

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

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 Cmax levels are likely to be observed in some children with a body weight below 10 kg.

Elderly

Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39 mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) obtained in nine studies with non-elderly adults after single doses of 30 to 450 mg.

Renal impairment

Twelve volunteers with chronic renal failure, and another six individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between hemodialysis) and 1.57 mL/min/kg (during hemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between hemodialysis) and 13.0 hours (during hemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour hemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections *Posology and method of administration* and *Special warnings and precautions for use*).

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 *Posology and method of administration*).

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

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

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

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

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

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC50 was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section *Pharmacodynamic properties*).

7 Description

Lamitor DT 25

White to off white round flat uncoated tablets.

Lamitor DT 50

White to off white round flat uncoated tablets.

Lamitor DT 100

White to off white round flat uncoated tablets.

8 Pharmaceutical particulars

8.1 Incompatibilities None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Available in blister pack of 15 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30ºC, protected from light and moisture Caution: Keep all tablets away from reach of children

9. Patient Counselling Information

LAMITOR TD

(Lamotrigine Dispersible Tablets I.P.)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

9.3 How to use Lamitor DT
9.4 Possible side effects
9.5 How to store Lamitor DT
9.6 Contents of the pack and other information

9.1 What Lamitor DT is and what it is used for

Lamitor DT belongs to a group of medicines called anti-epileptics. It is used as add on therapy for partial and secondary generalized tonic clonic seizures.

Lamitor DT treats seizures by blocking the signals in the brain that trigger seizures (fits).

9.2 What you need to know before you use Lamitor DT Do not use Lamitor:

- **if you are allergic** (hypersensitive) to lamotrigine or any of the other ingredients of this medicine.
- If this applies to you:
- Tell your doctor and don't take Lamitor DT.
- **Take special care with Lamitor DT**
- **Talk to your doctor before taking Lamitor DT:**
- **if you have any kidney problems**
- if you have ever **developed a rash** after taking lamotrigine or other medicines for epilepsy
- **if you have ever developed meningitis after taking lamotrigine** (read the description of these symptoms in Section 9.4 of this leaflet: Rare side effects)
- **if you are already taking medicine that contains lamotrigine.**
- **if you have a condition called Brugada syndrome.** Brugada syndrome is a genetic disease that results in abnormal electrical activity within the heart. ECG abnormalities which may lead to arrhythmias (abnormal heart rhythm) can be triggered by lamotrigine.

If any of these applies to you:

→ **Tell your doctor**, who may decide to lower the dose or that Lamitor DT is not suitable for you.

Important information about potentially life-threatening reactions

A small number of people taking Lamitor DT get an allergic reaction or potentially lifethreatening skin reaction, which may develop into more serious problems if they are not treated. These can include Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). You need to know the symptoms to look out for while you are taking Lamitor DT.

→ **Read the description of these symptoms in Section 9.4 of this leaflet** under '*Potentially life-threatening reactions: get a doctor's help straight away*'.

Haemophagocytic lymphohistiocytosis (HLH)

There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine.

→ **Contact your doctor immediately** if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state, disturbances of brain function).

Thoughts of harming yourself or suicide

People with bipolar disorder can sometimes have thoughts of harming themselves or committing suicide. If you have bipolar disorder, you may be more likely to think like this:

- when you first start treatment
- if you have previously had thoughts about harming yourself or about suicide

- if you are under 25 years old

If you have distressing thoughts or experiences, or if you notice that you feel worse or develop new symptoms while you're taking Lamitor DT:

→ See a doctor as soon as possible or go to the nearest hospital for help.

You may find it helpful to tell a family member, caregiver or close friend that you can become depressed or have significant changes in mood and ask them to read this leaflet. You might ask them to tell you if they are worried about your depression or other changes in your behaviour.

A small number of people being treated with anti-epileptics such as Lamitor DT have also had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

If you're taking Lamitor DT for epilepsy

The seizures in some types of epilepsy may occasionally become worse or happen more often while you're taking Lamitor DT. Some patients may experience severe seizures, which may cause serious health problems. If your seizures happen more often or if you experience a severe seizure while you're taking Lamitor DT: **→ See a doctor as soon as possible.**

Other medicines and Lamitor DT

Tell your doctor if you are taking, have recently taken or might take any other medicines including herbal medicines or other medicines bought without a prescription.

Your doctor needs to know if you are taking other medicines to treat epilepsy or mental health problems. This is to make sure you take the correct dose of Lamitor DT. These medicines include:

- **oxcarbazepine, felbamate, gabapentin, levetiracetam, pregabalin, topiramate or zonisamide,** used to treat **epilepsy**
- **lithium, olanzapine** or **aripiprazole** used to treat **mental health problems**
- **bupropion**, used to treat **mental health problems** or to **stop smoking**

→ Tell your doctor if you are taking any of these]

Some medicines interact with Lamitor DT or make it more likely that people will have side effects. These include:

valproate, used to treat **epilepsy** and **mental health problems carbamazepine**, used to treat **epilepsy** and **mental health problems phenytoin, primidone or phenobarbitone**, used to treat epilepsy **risperidone**, used to treat **mental health problems rifampicin**, which is an **antibiotic medicines** used to treat **Human Immunodeficiency Virus (HIV) infection** (a combination of lopinavir and ritonavir or atazanavir and ritonavir) **hormonal contraceptives**, such as **the Pill** (see below).

→ Tell your doctor if you are taking any of these or if you start or stop taking any.

Hormonal contraceptives (such as the Pill) can affect the way Lamitor DT works

Your doctor may recommend that you use a particular type of hormonal contraceptive or another method of contraception, such as condoms, a cap or coil. If you are using a hormonal contraceptive like the Pill, your doctor may take samples of your blood to check the level of Lamitor DT. If you are using a hormonal contraceptive or if you plan to start using one:

→ Talk to your doctor, who will discuss suitable methods of contraception with you.

Lamitor DT can also affect the way hormonal contraceptives work, although it's unlikely to make them less effective. If you are using a hormonal contraceptive and you notice any changes in your menstrual pattern, such as breakthrough bleeding or spotting between periods:

→ **Tell your doctor.** These may be signs that Lamitor DT is affecting the way your contraceptive is working.

Pregnancy and breast-feeding

→ If you are pregnant, think you may be pregnant or are planning to have a baby ask your doctor for advice before taking this medicine.

- **You should not stop treatment without discussing this with your doctor.** This is particularly important if you have epilepsy.
- Pregnancy may alter the effectiveness of Lamitor DT, so you may need blood tests and your dose of Lamitor DT may be adjusted.
- There may be a small increased risk of birth defects, including a cleft lip or cleft palate, if Lamitor DT is taken during the first 3 months of pregnancy.
- Your doctor may advise you to take extra folic acid if you're planning to become pregnant and while you're pregnant.

→ If you are breast-feeding or planning to breast-feed ask your doctor for advice before taking this medicine. The active ingredient of Lamitor DT passes into breast milk and may affect your baby. Your doctor will discuss the risks and benefits of breastfeeding while you're taking Lamitor DT and will check your baby from time to time, whether drowsiness, rash or poor weight gain occurs, if you decide to breast-feed. Inform your doctor if you observe any of these symptoms in your baby.

Driving and using machines

Lamitor DT can cause dizziness and double vision.

→ Don't drive or use machines unless you are sure you're not affected.

If you have epilepsy, talk to your doctor about driving and using machines.

9.3 How to use Lamitor DT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor if you are not sure.

How much Lamitor DT to take

It may take a while to find the best dose of Lamitor DT for you. The dose you take will depend on:

- your age
- whether you are taking Lamitor DT with other medicines
- whether you have any kidney or liver problems.

Your doctor will prescribe a low dose to start and gradually increase the dose over a few weeks until you reach a dose that works for you (called the effective dose).

Never take more Lamitor DT than your doctor tells you to.

The usual effective dose of Lamitor DT for adults and children aged 13 years or over is between 100 mg and 400 mg each day.

For children aged 2 to 12 years, the effective dose depends on their body weight - usually, it's between 1 mg and 15 mg for each kilogram of the child's weight, up to a maximum maintenance dose of 200 mg daily.

Lamitor DT is not recommended for children aged under 2 years.

How to take your dose of Lamitor DT

Take your dose of Lamitor DT once or twice a day, as your doctor advises. It can be taken with or without food.

- **Always take the full dose** that your doctor has prescribed. Never take only part of a tablet.

Your doctor may also advise you to start or stop taking other medicines, depending on what condition you're being treated for and the way you respond to treatment.

Direction for use: Disperse the tablet in 10ml of boiled and cooled water before administration.

If you take more Lamitor DT than you should

→ **Contact a doctor or nearest hospital emergency department immediately.** If possible, show them the Lamitor DT packet.

If you take too much **Lamitor DT you may be more likely to have serious side effects which may be fatal.**

Someone who has taken too much Lamitor DT may have any of these symptoms:

- rapid, uncontrollable eye movements (nystagmus)
- clumsiness and lack of co-ordination, affecting their balance (ataxia)
- heart rhythm changes (detected usually on ECG)
- loss of consciousness, fits (convulsions) or coma.

If you forget to take a single dose of Lamitor DT

→ Don't take extra tablets to make up for a missed dose. Just take your next dose at the usual time. In case you forget to take multiple doses of Lamitor DT.

→ **Ask your doctor for advice on how to start taking it again.** It's important that you do this.

Don't stop taking Lamitor DT without advice

Lamitor DT must be taken for as long as your doctor recommends. Don't stop unless your doctor advises you to.

If you're taking Lamitor DT for epilepsy

To stop taking Lamitor DT, it is important that the dose is reduced gradually, over about 2 weeks. If you suddenly stop taking Lamitor DT, your epilepsy may come back or get worse.

9.4 Possible Side Effects

Like all medicines, these tablets can cause side effects, although not everybody gets them.

Potentially life-threatening reactions: get a doctor's help straight away

A small number of people taking Lamitor DT get an allergic reaction or potentially lifethreatening skin reaction, which may develop into more serious problems if they are not treated.

These symptoms are more likely to happen during the first few months of treatment with Lamitor DT, especially if the starting dose is too high or if the dose is increased too quickly or if Lamitor DT is taken with another medicine called valproate. Some of the symptoms are more common in children, so parents should be especially careful to watch out for them.

Symptoms of these reactions include:

- **skin rashes or redness**, which may develop into life-threatening skin reactions including widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), extensive peeling of the skin (more than 30% of the body surface - toxic epidermal necrolysis) or extended rashes with liver, blood and other body organs involvement (Drug

Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS hypersensitivity syndrome)

- **ulcers in the mouth, throat, nose or genitals**
- **a sore mouth or red or swollen eyes** (conjunctivitis)
- **a high temperature** (fever), flu-like symptoms or drowsiness
- **swelling around your face or swollen glands** in your neck, armpit or groin **unexpected bleeding or bruising,** or the fingers turning blue **a sore throat** or more infections (such as colds) than usual
- Increased levels of liver enzymes seen in blood tests
- an increase in a type of white blood cell (eosinophils)
- enlarged lymph nodes
- involvement of the organs of the body including liver and kidneys.

In many cases, these symptoms will be signs of less serious side effects **but you must be aware that they are potentially life-threatening and can develop into more serious problems,** such as organ failure, if they are not treated. If you notice any of these symptoms:

→ **Contact a doctor immediately.** Your doctor may decide to carry out tests on your liver, kidneys or blood and may tell you to stop taking Lamitor DT. In case you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis your doctor will tell you that you must never use lamotrigine again.

Haemophagocytic lymphohistiocytosis (HLH) (see section: *What you need to know before you take Lamitor DT*).

Very common side effects

These may affect **more than 1 in 10** people:

- Headache
- skin rash

Common side effects

These may affect **up to 1 in 10** people:

- aggression or irritability
- feeling sleepy or drowsy
- feeling dizzy
- shaking or tremors
- difficulty in sleeping (insomnia)
- feeling agitated
- diarrhoea
- dry mouth
- feeling sick (nausea) or being sick (vomiting)
- feeling tired
- pain in your back or joints, or elsewhere.

Uncommon side effects

These may affect **up to 1 in 100** people:

clumsiness and lack of co-ordination (ataxia) double vision or blurred vision unusual hair loss or thinning (alopecia).

Rare side effects

These may affect **up to 1 in 1,000** people:

- a life-threatening skin reaction (Stevens-Johnson syndrome)
- a group of symptoms together including: fever, nausea, vomiting, headache, stiff neck and extreme sensitivity to bright light. This may be caused by an inflammation of the membranes that cover the brain and spinal cord (meningitis). These symptoms usually disappear once treatment is stopped however if the symptoms continue or get worse contact your doctor
- rapid, uncontrollable eye movements (nystagmus)
- itchy eyes, with discharge and crusty eyelids (conjunctivitis).

Very rare side effects

These may affect **up to 1 in 10,000** people:

- a life-threatening skin reaction (toxic epidermal necrolysis)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- a high temperature (fever)
- swelling around the face (oedema) or swollen glands in the neck, armpit or groin (lymphadenopathy)
- changes in liver function, which will show up in blood tests or liver failure
- a serious disorder of blood clotting, which can cause unexpected bleeding or bruising (disseminated intravascular coagulation)
- changes which may show up in blood tests - including reduced numbers of red blood cells (anaemia), reduced numbers of white blood cells (leucopenia, neutropenia, agranulocytosis), reduced numbers of 8 platelets (thrombocytopenia), reduced numbers of all these types of cell (pancytopenia) and a disorder of the bone marrow called aplastic anaemia
- hallucinations ('seeing' or 'hearing' things that aren't really there)
- confusion
- feeling 'wobbly' or unsteady when you move about
- uncontrollable body movements (tics), uncontrollable muscle spasms affecting the eyes, head and torso (choreoathetosis) or other unusual body movements such as jerking, shaking or stiffness in

people who already have epilepsy, seizures happening more often in people who already have Parkinson's disease, worsening of the symptoms.

lupus-like reaction (symptoms may include: back or joint pain which sometimes may be accompanied by fever and/or general ill health).

- Haemophagocytic lymphohistiocytosis (HLH) (see Section: *What you need to know before you take Lamitor DT*).

Other side effects

Other side effects have occurred in a small number of people but their exact frequency is unknown:

- There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor if you are on long-term anti-epileptic medication, have a history of osteoporosis or take steroids
- Nightmares
- Lower immunity because of lower levels of antibodies called immunoglobulins in the blood which help protect against infection

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Lamitor DT

- Keep out of the sight and reach of children.
- Store at a temperature not exceeding 30°C, protected from light and moisture.
- Do not use Lamitor DT after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information What Lamitor DT contains:

Lamitor DT 25mg

The active substance in this product is Lamotrigine.

The other ingredients are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

Lamitor DT 50mg

The active substance in this product is Lamotrigine.

The other ingredients are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

Lamitor DT 100mg

The active substance in this product is Lamotrigine.

The other ingredients are Sodium Saccharin, Trushil Tonovin Special, Calcium Carbonate, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone (K-30), Sodium Starch Glycollate, Magnesium Aluminium Silicate, Colloidal Silicon Dioxide (Aerosil), Aspartame.

10 Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No, Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

11 Details of permission or licence number with date

M/563/2010 dated 23.12.16

12 Date of revision

Apr-2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LAMITOR DT 25mg, 50mg, 100mg/Apr-2021/07/PI