carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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

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

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

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

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

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

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

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

Interactions involving other psychoactive agents

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

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and 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 Cmax of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the

single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100-400 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for a further 7 days. An average reduction of approximately 10% in Cmax and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

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

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, dosing with 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and 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 4.4). 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 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and 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 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the

appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and 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 4.2).

Data from in vitro assessment 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 a more potent in vitro inhibitor of OCT 2 than cimetidine, with IC50 values of 53.8 μM and 186 μM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

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 Pregnancy and lactation

Risk related to antiepileptic drugs in general

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs 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.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with AEDs compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple AEDs is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to lamotrigine

Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 2000 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 are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).

If therapy with Lamictal 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 (see section 4.4). 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. Among a limited group of exposed infants, no adverse effects were observed.

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

Fertility

Animal experiments did not reveal impairment of fertility by lamotrigine (see section 5.3).

4.7 Effects on ability to drive and use machines

As there is individual variation in response to all AED therapy, patients taking Lamictal 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. 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 adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how Lamictal therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects for epilepsy and bipolar disorder indications are based on available data from controlled clinical studies and other clinical experience and are listed in the table below. Frequency categories are derived from controlled clinical studies (epilepsy monotherapy (identified by†) and bipolar disorder (identified by §)). Where frequency categories differ between clinical trial data from epilepsy and bipolar disorder the most conservative frequency is shown. However, where no 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, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis	Very rare
	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
Psychiatric Disorders	Aggression, irritability	Common
	Confusion, hallucinations, tics	Very rare
Nervous System Disorders	Headache[§]	Very Common
	Somnolence[†§], dizziness[†§], tremor[†], insomnia[†] agitation[§]	Common
	Ataxia[†]	Uncommon
	Nystagmus[†]	Rare
	Unsteadiness, movement disorders, worsening of Parkinson's disease [3], extrapyramidal effects, choreoathetosis[†], increase in seizure frequency	Very Rare
	Aseptic meningitis (see section 4.4)	Rare
Eye disorders	Diplopia[†], blurred vision[†]	Uncommon
	Conjunctivitis	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†§]	Very common
	Stevens–Johnson Syndrome[§]	Rare
	Toxic epidermal necrolysis	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia[§]	Common
	Lupus-like reactions	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 Lamictal 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 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 macropapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamictal (see Section 4.4).

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 withdrawal of lamotrigine treatment, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

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

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

- concomitant use of valproate (see section 4.2).

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.

4.9 Overdose
Symptoms and signs

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

Treatment

In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. 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 5.2).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiepileptics, ATC code: N03AX09.

Mechanism of action

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.

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

Pharmacodynamic effects

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 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 at doses of 150 mg and 300 mg did not differ from placebo.

Clinical efficacy and safety in children aged 1 to 24 months

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 are 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 have 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.

Clinical efficacy in the prevention of mood episodes in patients with bipolar disorder

The efficacy of lamotrigine in the prevention of mood episodes in patients with bipolar I disorder has been evaluated in two studies.

Study SCAB2003 was a multicentre, double-blind, double dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or adjunctive therapy, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200, 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/L) or placebo for a maximum of 76 weeks (18 months). The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where the interventions were additional pharmacotherapy or electroconvulsive therapy (ECT). Study SCAB2006 had a similar design as study SCAB2003, but differed from study SCAB2003 in evaluating a flexible dose of lamotrigine (100 to 400 mg/day) and including patients with bipolar I disorder who had recently or were currently experiencing a manic episode. The results are shown in Table 7.

Table 7: Summary of results from studies investigating the efficacy of lamotrigine in the prevention of mood episodes in patients with bipolar I disorder

'Proportion' of patients being event free at week 76						
	Study SCAB2003 Bipolar I			**Study SCAB2006 Bipolar I**		
Inclusion criterion	Major depressive episode			Major manic episode		
	Lamotrigine	Lithium	Placebo	Lamotrigine	Lithium	Placebo
Intervention free	0.22	0.21	0.12	0.17	0.24	0.04
p-value Log rank test	0.004	0.006	-	0.023	0.006	-
Depression free	0.51	0.46	0.41	0.82	0.71	0.40
p-value Log rank test	0.047	0.209	-	0.015	0.167	-
Free of mania	0.70	0.86	0.67	0.53	0.64	0.37
p-value Log rank test	0.339	0.026	-	0.280	0.006	-

In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine-treated patients had significantly longer times to first depressive episode than placebo patients, and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

The efficacy of lamotrigine in combination with mood stabilisers has not been adequately studied.

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.

5.2 Pharmacokinetic properties

Absorption

Lamotrigine is rapidly and completely absorbed from the gut with no significant

first-pass metabolism. Peak plasma concentrations occur approximately 2.5 hours 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 glucuronidation-inducing 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 4.2).

Linearity

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

Special patient 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 4.2).

Infants aged 2 to 26 months

In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher 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 4.2 and 4.4).

Hepatic impairment

A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24 or 0.10 mL/min/kg in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared with 0.34 mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

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 5.1).

6. Pharmaceutical particulars

6.1 List of excipients

25, 50, 100 and 200 mg tablets:

Lactose monohydrate

Microcrystalline cellulose

Povidone K30

Sodium starch glycolate (Type A)

Iron oxide yellow (E172)

Magnesium stearate.

2, 5, 25, and 100 mg dispersible/chewable tablets:

Calcium carbonate

Low substituted hydroxypropyl cellulose

Aluminium magnesium silicate

Sodium starch glycolate (Type A)

Povidone K30

Saccharin sodium

Magnesium stearate

Blackcurrant flavour.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
25, 50, 100 and 200 mg tablets, 5, 25 and 100 mg dispersible/chewable tablets:

Three years.

2 mg dispersible/chewable tablets:

Two years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Lamictal 25 mg tablets: PVC/aluminium foil blister. Packs of 56 tablets.

Lamictal 50 mg tablets: PVC/aluminium foil blister. Packs of 56 tablets.

Lamictal 100 mg tablets: PVC/aluminium foil blister. Packs of 56 tablets.

Lamictal 200 mg tablets: PVC/aluminium foil blister. Packs of 56 tablets.

Lamictal 2 mg dispersible/chewable tablets: HDPE bottles with a child resistant/tamper evident closure.

Packs of 30 dispersible/chewable tablets.

Lamictal 5 mg dispersible/chewable tablets: PVC/PVdC/aluminium foil blister. Packs of 28 dispersible/chewable tablets.

Lamictal 25 mg dispersible/chewable tablets: PVC/PVdC/aluminium foil blister. Packs of 56 dispersible/chewable tablets.

Lamictal 100 mg dispersible/chewable tablets: PVC/PVdC/aluminium foil blister. Packs of 56 dispersible/chewable tablets.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. Marketing authorisation holder
The Wellcome Foundation Ltd

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Brentford

Middlesex TW8 9GS

United Kingdom

Trading as

GlaxoSmithKline UK

Stockley Park West

Uxbridge

Middlesex UB11 1BT

United Kingdom

8. Marketing authorisation number(s)
Lamictal 25 mg tablets: 00003/0272

Lamictal 50 mg tablets: 00003/0273

Lamictal 100 mg tablets: 00003/0274

Lamictal 200 mg tablets: 00003/0297

Lamictal 2 mg dispersible/chewable tablets: 00003/0375

Lamictal 5 mg dispersible/chewable tablets: 00003/0346

Lamictal 25 mg dispersible/chewable tablets: 00003/0347

Lamictal 100 mg dispersible/chewable tablets: 00003/0348

9. Date of first authorisation/renewal of the authorisation
Lamictal 25 mg tablets: 27 Aug 1997

Lamictal 50 mg tablets: 27 Aug 1997

Lamictal 100 mg tablets: 27 Aug 1997

Lamictal 200 mg tablets: 06 Sep 1999

Lamictal 2 mg dispersible/chewable tablets: 18 Dec 2000

Lamictal 5 mg dispersible/chewable tablets: 06 Sep 1999

Lamictal 25 mg dispersible/chewable tablets: 06 Sep 1999

Lamictal 100 mg dispersible/chewable tablets: 06 Sep 1999

10. Date of revision of the text
05 February 2013

Lamivudine Sandoz 100 mg Film-coated Tablets

1. Name of the medicinal product
Lamivudine Sandoz 100 mg Film-coated Tablets

2. Qualitative and quantitative composition
Each film-coated tablet contains 100 mg lamivudine.

Excipient with known effect: isomalt (E953)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet

Lamivudine Sandoz 100 mg Film-coated Tablets

Pink capsule shaped, biconvex, film coated tablets with a dimension of 12 x 6 mm, debossed with '37' on one side and 'I' on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Lamivudine is indicated for the treatment of chronic hepatitis B in adults with:

· compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis. Initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate (see in section 5.1).

· decompensated liver disease in combination with a second agent without cross-resistance to lamivudine (see section 4.2).

4.2 Posology and method of administration
Posology

Therapy with Lamivudine should be initiated by a physician experienced in the management of chronic hepatitis B.

Adults: the recommended dosage of Lamivudine is 100 mg once daily.

In patients with decompensated liver disease, lamivudine should always be used in combination with a second agent, without cross-resistance to lamivudine, to reduce the risk of resistance and to achieve rapid viral suppression.

Duration of treatment: The optimal duration of treatment is unknown.

· In patients with HBeAg positive chronic hepatitis B (CHB) without cirrhosis, treatment should be administered for at least 6-12 months after HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection) is confirmed, to limit the risk of virological relapse, or until HBsAg seroconversion or there is loss of efficacy (see section 4.4). Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

· In patients with HBeAg negative CHB (pre-core mutant) without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment, regular reassessment is recommended to confirm that continuation of the selected therapy remains appropriate for the patient.

· In patients with decompensated liver disease or cirrhosis and in liver transplant recipients, treatment cessation is not recommended (see section 5.1).

If Lamivudine is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see section 4.4).

Clinical resistance: In patients with either HBeAg positive or HBeAg negative CHB, the development of YMDD (tyrosine-methionine-aspartate-aspartate) mutant HBV may result in a diminished therapeutic response to lamivudine, indicated by a rise in HBV DNA and ALT from previous ontreatment levels. In order to reduce the risk of resistance in patients receiving lamivudine monotherapy, a modification of treatment should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment. In patients with YMDD mutant HBV, addition of an alternative agent without cross-resistance to lamivudine should be considered (see section 5.1).

Special populations

Paediatric population

The safety and efficacy of Lamivudine in children and adolescents aged below 18 years have not been established. Currently available data are described in sections 4.4 and 5.1 but no recommendation on a posology can be made.

Renal impairment

Lamivudine serum concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should therefore be reduced for patients with a creatinine clearance of < 50 ml/minute. When doses below 100 mg are required lamivudine oral solution should be used (see Table 1 below).

Table 1: Dosage of Lamivudine in patients with decreased renal clearance.

Creatinine clearance ml/min	**First Dose of lamivudine oral solution ***	**Maintenance Dose Once daily**
30 to < 50	20 ml (100 mg)	10 ml (50 mg)
15 to < 30	20 ml (100 mg)	5 ml (25 mg)
5 to < 15	7 ml (35 mg)	3 ml (15 mg)
< 5	7 ml (35 mg)	2 ml (10 mg)

* Lamivudine oral solution containing 5 mg/ml lamivudine.

Data available in patients undergoing intermittent haemodialysis (for less than or equal to 4 hrs dialysis 2-3 times weekly), indicate that following the initial dosage reduction of lamivudine to correct for the patient's creatinine clearance, no further dosage adjustments are required while undergoing dialysis.

Hepatic impairment

Data obtained in patients with hepatic impairment, including those with end-stage liver disease awaiting transplant, show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with hepatic impairment unless accompanied by renal impairment.

Method of administration

Lamivudine can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lamivudine has been administered to children (2 years and above) and adolescents with compensated chronic hepatitis B. However, due to limitations of the data, the administration of lamivudine to this patient population is not currently recommended (see section 5.1).

The efficacy of lamivudine in patients co-infected with Delta hepatitis or hepatitis C has not been established and caution is advised.

Data are limited on the use of lamivudine in HBeAg negative (pre-core mutant) patients and in those receiving concurrent immunosuppressive regimes, including cancer chemotherapy. Lamivudine should be used with caution in these patients.

During treatment with Lamivudine patients should be monitored regularly. Serum ALT and HBV DNA levels should be monitored at 3 month intervals and in HBeAg positive patients HBeAg should be assessed every 6 months.

Exacerbations of hepatitis

Exacerbations on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline. In patients with compensated liver disease, these increases in serum ALT were generally not accompanied by an increase in serum bilirubin concentrations or signs of hepatic decompensation.

HBV viral subpopulations with reduced susceptibility to lamivudine (YMDD mutant

HBV) have been identified with extended therapy. In some patients the development of YMDD mutant HBV can lead to exacerbation of hepatitis, primarily detected by serum ALT elevations and re-emergence of HBV DNA (see section 4.2). In patients who have YMDD mutant HBV, addition of a second agent without cross resistance to lamivudine, should be considered (see section 5.1).

Exacerbations after treatment discontinuation: Acute exacerbation of hepatitis has been observed in patients who have discontinued hepatitis B therapy and is usually detected by serum ALT elevations and re-emergence of HBV DNA. In the controlled Phase III trials with no-active-treatment follow-up, the incidence of post-treatment ALT elevations (more than 3 times baseline) was higher in lamivudine-treated patients (21%) compared with those receiving placebo (8%). However, the proportion of patients who had post-treatment elevations associated with bilirubin elevations was low and similar in both treatment arms. See Table 3 in section 5.1 for more information regarding frequency of post treatment ALT elevations. For lamivudine-treated patients, the majority of posttreatment ALT elevations occurred between 8 and 12 weeks post-treatment. Most events have been self-limiting, however some fatalities have been observed. If Lamivudine is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months, and then as clinically indicated.

Exacerbations in patients with decompensated cirrhosis: Transplantation recipients and patients with decompensated cirrhosis are at greater risk from active viral replication. Due to the marginal liver function in these patients, hepatitis reactivation at discontinuation of lamivudine or loss of efficacy during treatment may induce severe and even fatal decompensation. These patients should be monitored for clinical, virological and serological parameters associated with hepatitis B, liver and renal function, and antiviral response during treatment (at least every month), and, if treatment is discontinued for any reason, for at least 6 months after treatment. Laboratory parameters to be monitored should include (as a minimum) serum ALT, bilirubin, albumin, blood urea nitrogen, creatinine, and virological status: HBV antigen/antibody, and serum HBV DNA concentrations when possible. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored more frequently as appropriate.

For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of lamivudine treatment.

HIV co-infection

For the treatment of patients who are co-infected with HIV and are currently receiving or plan to receive treatment with lamivudine or the combination lamivudine-zidovudine, the dose of lamivudine prescribed for HIV infection (usually 150 mg/twice daily in combination with other antiretrovirals) should be maintained. For HIV co-infected patients not requiring anti-retroviral therapy, there is a risk of HIV mutation when using lamivudine alone for treating chronic hepatitis B.

Transmission of hepatitis B

There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with lamivudine. The standard recommended

procedures for hepatitis B virus immunisation in infants should be followed.

Patients should be advised that therapy with lamivudine has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

Lactic acidosis and severe hepatomegaly with steatosis

Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As Lamivudine is a nucleoside analogue, this risk cannot be excluded. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribivirin may constitute a special risk. These patients should be followed closely.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). The neurological disorders might be transient or permanent. Any child exposed in utero to nucleoside and nucleotide analogues, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in cases which have relevant signs or symptoms.

Fructose intolerance

Patients with rare hereditary problems of fructose intolerance should not take this medicine

Lamivudine should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

The likelihood of metabolic interactions is low due to limited metabolism and plasma

protein binding and almost complete renal elimination of unchanged substance.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine. Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased lamivudine exposure by about 40 %. Lamivudine had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary.

A modest increase in Cmax (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine (see section 5.2).

Lamivudine has no pharmacokinetic interaction with alpha-interferon when the two medicinal products are concurrently administered. There were no observed clinically significant adverse interactions in patients taking lamivudine concurrently with commonly used immunosuppressant medicinal products (e.g. cyclosporin A). However, formal interaction studies have not been performed.

Cladribine: In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Lamivudine can be used during pregnancy if clinically needed.

For patients who are being treated with lamivudine and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Breast-feeding

Based on more than 130 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (about 0.06 to 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. The total amount of lamivudine ingested by a breastfed infant is very low and is therefore likely to result in exposures exerting a sub-optimal antiviral effect. Maternal hepatitis B is not a contraindication to breast-feeding if the newborn is adequately managed for hepatitis B prevention at birth, and there is no evidence that the low concentration of lamivudine in human milk leads

to adverse events in breastfed infants. Therefore breastfeeding may be considered in lactating mothers being treated with lamivudine for HBV taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Where there is maternal transmission of HBV, despite adequate prophylaxis, consideration should be given to discontinuing breastfeeding to reduce the risk of the emergence of lamivudine resistant mutants in the infant.

Fertility

No data available.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The incidence of adverse reactions and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) were similar between placebo and lamivudine treated patients). The most common adverse reactions reported were malaise and fatigue, respiratory tract infections, throat and tonsil discomfort, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea.

Adverse reactions are listed below by system organ class and frequency. Frequency categories are only assigned to those adverse reactions considered to be at least possibly causally related to lamivudine. Frequencies are defined as: 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) and not known (cannot be estimated from the available data).

The frequency categories assigned to the adverse reactions are mainly based on experience from clinical trials including a total of 1171 patients with chronic hepatitis B receiving lamivudine at 100mg.

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Rare	Angioedema
Hepatobiliary disorders	
Very common	ALT elevations (see section 4.4)
Exacerbations of hepatitis, primarily detected by serum ALT elevations, have been reported 'on treatment' and following lamivudine withdrawal. Most events have been self-limited, however fatalities have been observed very rarely (see section 4.4).	