General disorders and administration site conditions

Common: Fatigue, malaise, fever.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (cART). The frequency of which is unknown (see section 4.4).

4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC Code: J05AF05.

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication in vitro, it is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show

diminished viral replicative capacity in vitro. In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. In vitro susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells in vitro.

Clinical experience:

In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the M184V mutations.

The relationship between in vitro susceptibility of HIV to lamivudine and clinical response to lamivudine-containing therapy remains under investigation.

Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for Zeffix). However, for the treatment of HIV infection only a 300 mg daily dose of lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.

Once daily dosing (300 mg once a day): a clinical study has demonstrated the non

inferiority between Epivir once a day and Epivir twice a day containing regimens. These results were obtained in an antiretroviral naïve-population, primarily consisting of asymptomatic HIV infected patients (CDC stage A).

5.2 Pharmacokinetic properties

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (tmax) to maximal serum concentrations (Cmax) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state Cmax and Cmin of lamivudine in plasma are 1.2 μg/ml (24%) and 0.09 μg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 μg.h/ml (18%). At a therapeutic dose of 300mg once daily, the mean (CV) steady-state Cmax, Cmin and 24h AUC are 2.0 μg/ml (26%), 0.04 μg/ml (34%) and 8.9 μg.h/ml (21%), respectively.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, Cmax, and tmax.

Co-administration of lamivudine with food results in a delay of tmax and a lower C max (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Distribution

From intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16% - 36% to serum albumin in in vitro studies).

Limited data show that lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Epivir 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to Epivir 150 mg twice daily with

respect to intracellular triphosphate AUC24 and Cmax.

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.

Elimination

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section (see section 4.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Pharmacokinetics in children: In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice daily. This dose will achieve an average AUC0-12 ranging from approximately 3,800 to 5,300 ng.h/ml. Recent findings indicate that exposure in children < 6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetics in pregnancy: Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant women.

5.3 Preclinical safety data

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed in in vivo tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Microcrystalline cellulose (E460),

Sodium starch glycollate

Magnesium stearate

Tablet film-coat:

Hypromellose (E464)

Titanium dioxide (E171),

Macrogol,

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE bottles:
5 years

PVC/aluminium foil blister packs:
2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Child resistant HDPE bottles or PVC/aluminium foil blister packs each containing 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. Marketing authorisation holder
ViiV Healthcare UK Limited

980 Great West Road

Brentford

Middlesex

TW8 9GS

United Kingdom

8. Marketing authorisation number(s)
EU/1/96/015/001 (Bottle)

EU/1/96/015/004 (Blister pack)

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 8 August 1996

Date of last renewal: 28 July 2006

10. Date of revision of the text
25 April 2013

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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Lamictal
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1. Name of the medicinal product

Lamictal 25 mg tablets.

Lamictal 50 mg tablets.

Lamictal 100 mg tablets.

Lamictal 200 mg tablets.

Lamictal 2 mg dispersible/chewable tablets.

Lamictal 5 mg dispersible/chewable tablets.

Lamictal 25 mg dispersible/chewable tablets.

Lamictal 100 mg dispersible/chewable tablets.

2. Qualitative and quantitative composition

Each Lamictal 25 mg tablet contains 25 mg lamotrigine.

Excipient: Each tablet contains 23.5 mg lactose.

Each Lamictal 50 mg tablet contains 50 mg lamotrigine.

Excipient: Each tablet contains 46.9 mg lactose.

Each Lamictal 100 mg tablet contains 100 mg lamotrigine.

Excipient: Each tablet contains 93.9 mg lactose.

Each Lamictal 200 mg tablet contains 200 mg lamotrigine.

Excipient: Each tablet contains 109.0 mg lactose.

Each Lamictal 2 mg dispersible/chewable tablet contains 2 mg lamotrigine.

Each Lamictal 5 mg dispersible/chewable tablet contains 5 mg lamotrigine.

Each Lamictal 25 mg dispersible/chewable tablet contains 25 mg lamotrigine.

Each Lamictal 100 mg dispersible/chewable tablet contains 100 mg lamotrigine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet.

Dispersible/chewable tablet.

25 mg tablets:

Pale, yellowish brown, multifaceted, super elliptical tablet, marked "GSEC7" on one side and "25" on the other.

50 mg tablets:

Pale, yellowish brown, multifaceted, super elliptical tablet, marked "GSEE1" on one side and "50" on the other.

100 mg tablets:

Pale, yellowish brown, multifaceted, super elliptical tablet, marked "GSEE5" on one side and "100" on the other.

200 mg tablets:

Pale, yellowish brown, multifaceted, super elliptical tablet, marked "GSEE7" on one side and "200" on the other.

2 mg dispersible/chewable tablets:

White to off white round tablet with a blackcurrant odour. One side has a bevelled edge and is marked "LTG" above the number 2. The other side is marked with two overlapping super ellipses at right angles. The tablets may be slightly mottled.

5 mg dispersible/chewable tablets:

White to off white, elongated, biconvex tablet with a blackcurrant odour, marked "GS CL2" on one side and "5" on the other. The tablets may be slightly mottled.

25 mg dispersible/chewable tablets:

White to off white multi faceted, super elliptical, tablet with a blackcurrant odour, marked "GSCL5" on one side "25" on the other. The tablets may be slightly mottled.

100 mg dispersible/chewable tablets:

White to off white multi faceted, super elliptical, tablet with a blackcurrant odour, marked "GSCL7" on one side and "100" on the other. The tablets may be slightly mottled.

4. Clinical particulars

4.1 Therapeutic indications
Epilepsy

Adults and adolescents aged 13 years and above

- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

- Seizures associated with Lennox-Gastaut syndrome. Lamictal is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

Children and adolescents aged 2 to 12 years

- Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

- Monotherapy of typical absence seizures.

Bipolar disorder

Adults aged 18 years and above

- Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

Lamictal is not indicated for the acute treatment of manic or depressive episodes.

4.2 Posology and method of administration
Lamictal tablets should be swallowed whole, and should not be chewed or crushed.

Lamictal dispersible/chewable tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

If the calculated dose of lamotrigine (for example for treatment of children with epilepsy or patients with hepatic impairment) does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

Restarting therapy

Prescribers should assess the need for escalation to maintenance dose when restarting Lamictal in patients who have discontinued Lamictal 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 4.4). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see section 5.2), Lamictal should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that Lamictal 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 (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the

effect this may have on lamotrigine pharmacokinetics (see section 4.5).

Table 1: Adults and adolescents aged 13 years and above – recommended treatment regimen in epilepsy

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy:	25 mg/day (once a day)	50 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 50 - 100 mg every one to two weeks until optimal response is achieved 500 mg/day has been required by some patients to achieve desired response
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5)**:**			
This dosage regimen should be used with valproate regardless of any concomitant medicinal products	12.5 mg/day (given as 25 mg 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 4.5)**:**			
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 4.5)**:**			
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	25 mg/day (once a day)	50 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 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 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

Table 2: 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
Monotherapy of typical absence seizures:	0.3 mg/kg/day (once a day or two	0.6 mg/kg/day (once a day or two	1 – 15 mg/kg/day (once a day or two divided

	divided doses)	divided doses)	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 maintenance dose of 200mg/day
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5)**:**			
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 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 4.5)**:**			
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 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 4.5)**:**			
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 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 4.5), 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 Lamictal 2 mg dispersible/chewable 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 Lamictal 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 Lamictal 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 4.4). There are no data in children below 1 month of age. Thus Lamictal 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 4.4, 5.1 and 5.2.

Bipolar disorder

The recommended dose escalation and maintenance doses for adults of 18 years of age and above are given in the tables below. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks (Table 3) after which other psychotropic medicinal products and/or AEDs can be withdrawn, if clinically indicated (Table 4). The dose adjustments following addition of other psychotropic medicinal products and/or AEDs are also provided below (Table 5). Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

Table 3: Adults aged 18 years and above - recommended dose escalation to the maintenance total daily stabilisation dose in treatment of bipolar disorder

Treatment Regimen	Weeks 1 + 2	Weeks 3 + 4	Week 5	Target Stabilisation Dose (Week 6)*
Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):				
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day (once a day or two divided doses)	200 mg/day - usual target dose for optimal response (once a day or two divided doses) Doses in the range 100 - 400 mg/day used in clinical trials
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):				
This dosage regimen should be used with valproate regardless of any concomitant medicinal products	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day - usual target dose for optimal response (once a day or two divided doses) Maximum dose of 200 mg/day can be used depending on clinical response
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):				
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 mg/day (two divided doses)	300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not				

known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

* The Target stabilisation dose will alter depending on clinical response

Table 4: Adults aged 18 years and above - maintenance stabilisation total daily dose following withdrawal of concomitant medicinal products in treatment of bipolar disorder

Once the target daily maintenance stabilisation dose has been achieved, other medicinal products may be withdrawn as shown below.

Treatment Regimen	Current lamotrigine stabilisation dose (prior to withdrawal)	Week 1 (beginning with withdrawal)	Week 2	Week 3 onwards *
Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:				
When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week	100 mg/day	200 mg/day	Maintain this dose (200 mg/day) (two divided doses)	
	200 mg/day	300 mg/day	400 mg/day	Maintain this dose (400 mg/day)
Withdrawal of inducers of lamotrigine glucuronidation (see section 4.5), depending on original dose of lamotrigine:				
This dosage regimen should be used when the following are withdrawn: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	400 mg/day	400 mg/day	300 mg/day	200 mg/day
	300 mg/day	300 mg/day	225 mg/day	150 mg/day
	200 mg/day	200 mg/day	150 mg/day	100 mg/day
Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):				
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn	Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 - 400 mg/day)			
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response .				

* Dose may be increased to 400 mg/day as needed

Table 5: Adults aged 18 years and above - adjustment of lamotrigine daily dosing following the addition of other medicinal products in treatment of bipolar disorder

There is no clinical experience in adjusting the lamotrigine daily dose following the addition of other medicinal products. However, based on interaction studies with other medicinal products, the following recommendations can be made:

Treatment Regimen	Current lamotrigine stabilisation dose (prior to addition)	Week 1 (beginning with addition)	Week 2	Week 3 onwards
Addition of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:				

This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products	200 mg/day	100 mg/day	Maintain this dose (100 mg/day)	
	300 mg/day	150 mg/day	Maintain this dose (150 mg/day)	
	400 mg/day	200 mg/day	Maintain this dose (200 mg/day)	
Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate (see section 4.5), depending on original dose of lamotrigine**:**				
This dosage regimen should be used when the following are added without valproate: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir	200 mg/day	200 mg/day	300 mg/day	400 mg/day
	150 mg/day	150 mg/day	225 mg/day	300 mg/day
	100 mg/day	100 mg/day	150 mg/day	200 mg/day
Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5)**:**				
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added	Maintain target dose achieved in dose escalation (200 mg/day; dose range 100-400 mg/day)			
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.				

Discontinuation of Lamictal in patients with bipolar disorder

In clinical trials, there was no increase in the incidence, severity or type of adverse reactions following abrupt termination of lamotrigine versus placebo. Therefore, patients may terminate Lamictal without a step-wise reduction of dose.

Children and adolescents below 18 years

Lamictal is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy (see section 4.4).

General dosing recommendations for Lamictal 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 two-fold) 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 4.4 and 4.5).

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 4.4 and 4.5). 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 4.4 and 4.5).

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 4.4 and 4.5). 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 4.5).

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 4.5).

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 non-elderly adult population (see section 5.2).

Renal impairment

Caution should be exercised when administering Lamictal 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 4.4 and 5.2).

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 5.2).

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

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 and toxic epidermal necrolysis (see section 4.8).

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 epileptic 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 4.2)

- concomitant use of valproate (see section 4.2).

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 Lamictal withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that Lamictal 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 or TEN with the use of lamotrigine, treatment with lamotrigine must not be restarted 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 4.8). 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.

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.

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 Lamictal. Therefore patients receiving Lamictal 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 4.5). 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 "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

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

Effects of lamotrigine on hormonal contraceptive efficacy

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 4.5). 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 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal failure

In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

Patients taking other preparations containing lamotrigine

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

25, 50, 100 and 200 mg tablets:

Excipient of Lamictal tablets

Lamictal 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.

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 Lamictal may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamictal 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.

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

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.

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

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Table 6: 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	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbitone	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate
	Ethinyloestradiol/ levonorgestrel combination**	Zonisamide
	Atazanavir/ritonavir*	Lithium
		Buproprion
		Olanzapine
		Aripiprazole

*For dosing guidance (see section 4.2)

**Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see sections 4.2 and 4.4).

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 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and 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 4.2).

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