Public Assessment Report

Mutual Recognition Procedure

Lamotrigine 25mg Tablets
Lamotrigine 50mg Tablets
Lamotrigine 100mg Tablets
Lamotrigine 200mg Tablets

UK/H/835/01-04
UK licence no: PL 00289/0500-3

TEVA UK Limited
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## Module 1

| **Product Name** | Lamotrigine 25mg Tablets  
| | Lamotrigine 50mg Tablets  
| | Lamotrigine 100mg Tablets  
| | Lamotrigine 200mg Tablets  
| **Type of Application** | Generic, Article 10.1  
| **Active Substance** | Lamotrigine  
| **Form** | Tablets  
| **Strength** | 25mg, 50mg, 100mg and 200mg Tablets  
| **MA Holder** | TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG  
| **RMS** | UK  
| **CMS** | Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Slovakia and Sweden  
| **Procedure Number** | UK/H/835/01-04  
| **Timetable** | Day 90 – 14th March 2006 (End of referral 9th June 2006)  

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25 mg lamotrigine.

Excipient: 18 mg lactose monohydrate/tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Lamotrigine 25 mg Tablets are white to off white, diamond-shaped tablet, debossed with the number “93” on one side and scored between the two numbers, debossed “39” on the other side of the tablet. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Epilepsy

Adults and adolescents
Monotherapy of:
- Partial epilepsy with or without generalisation
- Primary generalised epilepsy

Monotherapy in children under 12 years of age is not recommended.

Add on therapy in epilepsy:
- Partial seizures
- Generalised seizures:
  - primary seizures
  - secondary tonic-clonic seizures
- Seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic agent combinations fail.

Children over 2 years of age
Add-on therapy in:
- Partial seizures
- Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fails.

This medicinal product should only be started by a neurologist or paediatric neurologist with experience in the treatment of epilepsy or used in departments of neurology and similar departments.

4.2 Posology and method of administration
To achieve the maintenance dose, the weight of a patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine is not equal to whole tablets, the dose to be administered should be that of the lower number of whole tablets.

For doses not realisable/practicable with this medicinal product, other strengths of this medicinal product or other pharmaceutical forms and products are available.
When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with lamotrigine, or other AEDs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

**Dosage in monotherapy**

*Adults and adolescents*

The initial lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 mg-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.

### Table 1: Recommended dose escalation of lamotrigine for adults and adolescents on monotherapy.

<table>
<thead>
<tr>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks</td>
</tr>
</tbody>
</table>

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

**Dosage in add-on therapy**

*Adults and adolescents*

In patients taking valproate with / without any other AED the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 – 400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100-200 mg/day given once a day or in two divided doses.

### Table 2: Recommended dose escalation of lamotrigine for adults and adolescents on combined therapy.

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>12.5 mg (given as 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 25-50 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>50 mg (once a day)</td>
<td>100 mg (two divided doses)</td>
<td>200-400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors See section 4.5</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see section 4.4).

Children aged 2 to 12 years
In patients taking valproate with / without any other AED, the initial lamotrigine dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses, with a maximum dose of 400 mg/day.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

Table 3: Recommended dose escalation of lamotrigine for children aged 2-12 years on combined therapy (Total daily dose in mg/kg bodyweight/day)

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>0.15 mg/kg ** (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (two divided doses), up to a maximum dose of 400 mg/day</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors</td>
<td>0.3 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or in two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

**NOTE: The recommended dosing schedule for children may not be achievable with the current strengths of the tablets.

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

It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

Adults and children over 2 years of age
(Add-on therapy of Lennox-Gastaut syndrome if treatment with other available combinations of antiepileptic agents fail)
See above-mentioned dosing schedules.

Children aged less than 2 years
There is insufficient information on the use of lamotrigine in children aged less than 2 years.
**Elderly**
No dosage adjustment from recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly population.

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

**Renal impairment**
Caution should be exercised when administering lamotrigine 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).

**Combination with (continuous) oral hormonal contraceptives**
It is recommended to use continuous contraceptives in patients already taking maintenance doses of lamotrigine and starting oral hormonal contraceptives (see sections 4.4 and 4.5).

The following situations may occur:

(a) *Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:*
When starting hormonal contraceptives, in most cases the maintenance dose of lamotrigine may need to be increased by as much as two-fold (see sections 4.4 and 4.5). Lamotrigine plasma concentrations should be measured before and after starting hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. Dose escalation should follow the recommended dosing schedule.

(b) *Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:*
In most cases, the maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual clinical response (see sections 4.4 and 4.5). Adjustment of the dose should also be established in accordance with the individual plasma concentration of lamotrigine and/or the clinical response (the occurrence of dose-related adverse effects). Lamotrigine plasma concentrations should be measured before and after stopping hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. After stopping hormonal contraceptives, it is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg a week over a period of 3 weeks.

(c) *Starting lamotrigine in patients already taking continuous hormonal contraceptives:*
The recommended dosing schedules should be used (see Tables 1 and 2).

**Pregnancy**
See section 4.6.

**Re-starting therapy**
The need for escalation to maintenance dose should be carefully assessed when re-starting lamotrigine in patients who have discontinued it, 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), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy.

**Method of administration**
The tablets should be swallowed whole with a little water, and should be taken as far as possible at the same time every day, on an empty stomach or with a meal.

**4.3 Contraindications**
Lamotrigine is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients.
4.4 Special warnings and precautions for use

Due to possible cross-reactions, lamotrigine should be administered with special precaution in individuals with known hypersensitivity to carbamazepine and phenytoin.

The switching of patients between lamotrigine products from different sources is to be avoided without prior consideration by the clinician.

Skin reactions

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however, rarely serious potentially life threatening skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence of children under the age of 12 requiring hospitalisation due to rash is from 1 in 300 to 1 in 100 (see section 4.8).

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a medicinal product reaction 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, which increases the mean half-life of lamotrigine nearly two-fold (see section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not product-related.

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 (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Withdrawal of lamotrigine

Abrupt withdrawal of lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

Potential pharmacokinetic interactions should be taken into consideration in case of any alteration in treatment (e.g. the introduction or withdrawal of other antiepileptic agents, see sections 4.2 and 4.5). Lamotrigine can increase attacks in some patients.

Other organs

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

Folic acid metabolism

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

Use in combination with hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyl-oestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold (see section 4.5). A decrease in lamotrigine plasma concentration was associated with loss of control of epileptic attacks. Following dose escalation, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. This has been associated with dose-related unwanted effects. 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 (e.g. ‘pill-free week’), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive treatment. After starting the hormonal contraceptive treatment again the lamotrigine levels will decrease. Variations in lamotrigine levels of this order are not recommended.

Therefore, although it has not been evaluated whether these increases or decreases in lamotrigine levels can lead to the occurrence of dose-related undesirable effects or a loss of control of epileptic attacks, respectively, it is recommended that patients on maintenance doses of lamotrigine and starting hormonal contraceptives use a continuous hormonal contraceptive and not those that include a week of inactive medicinal product.

Other hormonal contraceptive and hormone replacement therapy (HRT) treatments 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 (ethinyl-oestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum follicle-stimulating hormone (FSH) and luteinising hormone (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, e.g. breakthrough bleeding.

**Renal impairment**
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.

**Hepatic impairment**
In patients with moderate (Child-Pugh grade B) and severe (Child-Pugh grade C) hepatic impairment it has been shown that initial, escalation and maintenance doses should be reduced (see section 4.2). Caution should be exercised when dosing this hepatically impaired population.

**Women of childbearing age**
Women of childbearing age and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations may be enhanced in combination therapy with other anticonvulsants.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**4.5 Interaction with other medicinal products and other forms of interaction**
UDP-glucuronol 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 substance-metabolising enzymes, and interactions between lamotrigine and substances metabolised by cytochrome P450 (CYP) enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

**Effect of lamotrigine on the pharmacokinetics of other active substances**
*Antiepileptics*
There have been reports of central nervous system events including headache, nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

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 antiepileptic drugs from protein binding sites.

**Hormonal contraceptives**

Effect of lamotrigine on hormonal contraceptives:
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 hormonal contraceptive pill. A modest increase in overall clearance of the levonorgestrel component was observed. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. 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.

**Effect of other active substances on the pharmacokinetics of lamotrigine**
Antiepileptic agents which induce substance-metabolising enzymes in the liver (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). The half-life of lamotrigine is shortened to approximately 14 hours; in children below 12 years, approximately 7 hours.

Sodium valproate, which competes with lamotrigine for hepatic substance-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two fold. The half-life of lamotrigine is extended to approx. 70 hours; in children below 12 years, 45-55 hours.

**Table 4: Effects of other active substances on glucuronidation of lamotrigine**

<table>
<thead>
<tr>
<th>Active substances that significantly inhibit glucuronidation of lamotrigine</th>
<th>Active substances that significantly induce glucuronidation of lamotrigine</th>
<th>Active substances that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Oxcarbazepine**</td>
</tr>
</tbody>
</table>
| | Rifampicin*** | *
| | Ethinyloestradiol/levonorgestrel combination* | |

* Other hormonal contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.
** In a study in healthy adult volunteers using doses of 200 mg/day lamotrigine and 1200 mg/day oxcarbazepine, results showed that compared with placebo, the mean values for steady state peak plasma concentration (C_max) and area under the curve (AUC_0-24) of lamotrigine were reduced by 2% and 8%, respectively. The 90% confidence intervals indicated that the differences were between -22% and +8% for AUC_0-24 and -15% and +15% for C_max. Adverse events were reported more frequently with oxcarbazepine and lamotrigine than with either monotherapy. The most common undesirable effects were headache, dizziness, nausea and somnolence.
*** In a study in 10 healthy adult males, rifampicin increased the clearance and shortened the half-life of lamotrigine.

**Hormonal contraceptives**

Effect of hormonal contraceptives on lamotrigine:
In a study of 16 female volunteers, 30 mcg ethinyloestradiol/150 mcg levonorgestrel in a combined hormonal contraceptive pill caused an approximately two-fold increase in lamotrigine overall clearance, resulting in an average 52% and 39% reduction in lamotrigine area under the curve (AUC) and C_max, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive treatment (e.g. "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.
If the therapeutic effect of lamotrigine is uncertain although dose adjustments have been made, a non-hormonal contraceptive method could be considered.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during lamotrigine therapy.

**Psychoactive medicines**

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

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

Multiple oral doses of 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 vitro** inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-\( N \)-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of active substances eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. However it has been reported that sertraline may increase the toxicity of lamotrigine by increasing the plasma concentration of lamotrigine.

**Folic acid**

Interaction with folic acid metabolism (see sections 4.4 and 4.6).

During prolonged human lamotrigine dosing, there were no significant changes in haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folic acid concentrations up to 1 year or red blood cell folic acid concentration up to 5 years.

### 4.6 Pregnancy and lactation

**Pregnancy**

**Risk related to epilepsy and antiepileptic agents in general**

It is known that newborn children from mothers who use antiepileptic products or suffer from epilepsy more frequently have development disorders, such as cardiac abnormalities and cranial facial disorders, than other babies. Multiple antiepileptic therapy during pregnancy may increase the risk of fetal malformations and should therefore be avoided, unless it appears justified after having assessed the risk-benefit ratio.

**Risk linked to lamotrigine**

There are limited data available on the use of lamotrigine during pregnancy. Lamotrigine passes through the placenta, since plasma concentrations in some newborns were at therapeutic levels. Lamotrigine should not be used in pregnancy, unless the potential benefits of treatment to the mother outweigh any possible risks to the developing fetus. Reduction or discontinuation of seizure prophylaxis may carry considerable risk for both mother and fetus that is probably greater than any risk of malformation.

Animal experiments have shown no evidence of teratogenic effects (see section 5.3).

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

Furthermore, it is important that pregnant women and women of child-bearing potential practice monotherapy whenever possible.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during lamotrigine therapy should be ensured.
Lamotrigine plasma levels should therefore be monitored before, during and after pregnancy, as well as during birth. If necessary, the dose should be adapted, to maintain the lamotrigine plasma concentration on the same level as before pregnancy. In addition, dose-related adverse effects should be monitored after birth.

**Lactation**

Lamotrigine is excreted into breast milk and may reach serum concentrations in the breast-fed infant that are in the usual therapeutic range in the mother. Mothers should therefore breast-feed only after a careful risk-benefit assessment for the infant. If the infant is breast-fed, he/she should be monitored for possible effects.

**4.7 Effects on ability to drive and use machines**

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo.

In clinical trials with lamotrigine adverse effects of a neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all AED therapy patients should consult their physician on the specific issues of driving and epilepsy.

**4.8 Undesirable effects**

The following convention has been utilised for the classification of undesirable effects:

- Very common (≥1/10)
- Common (≥1/100 and <1/10)
- Uncommon (≥1/1000 and <1/100)
- Rare (≥1/10,000 and <1/1000)
- Very rare (≤1/10,000, including isolated reports)

**Table 5: Undesirable Effects**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Blood and lymphatic system disorders</em></td>
<td></td>
<td></td>
<td></td>
<td>Haematological abnormalities²</td>
</tr>
<tr>
<td><em>Immune system disorders</em></td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity syndrome</td>
</tr>
<tr>
<td><em>Psychiatric disorders</em></td>
<td>Irritability</td>
<td>Aggression</td>
<td></td>
<td>Tics, hallucinations, confusion</td>
</tr>
<tr>
<td><em>Nervous system disorders</em></td>
<td></td>
<td></td>
<td></td>
<td>Agitation, unsteadiness, movement disorders, worsening of Parkinson’s disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency³</td>
</tr>
<tr>
<td>Headache, dizziness</td>
<td>Drowsiness, insomnia, tremor, nystagmus, ataxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Eye disorders</em></td>
<td></td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Dioplia, blurred vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Gastrointestinal disorders</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbance, nausea, vomiting, diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hepato-biliary disorders</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased liver function tests, hepatic dysfunction, hepatic failure(^4)</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Skin rash(^1)</th>
<th>Stevens Johnson syndrome</th>
<th>Toxic epidermal necrolysis</th>
</tr>
</thead>
</table>

**Musculoskeletal, connective tissue and bone disorders**

<table>
<thead>
<tr>
<th>Lupus-like reactions</th>
</tr>
</thead>
</table>

**General disorders**

<table>
<thead>
<tr>
<th>Tiredness</th>
</tr>
</thead>
</table>

\(^1\)In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4).

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

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence in children under the age of 12 requiring hospitalisation due to rash ranges from 1 in 300 to 1 in 100 (see section 4.4).

In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a reaction 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).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related.

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 (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

\(^2\)Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis) may or may not be associated with the hypersensitivity syndrome.

\(^3\)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.
There are insufficient data available about the effect of lamotrigine on growth, development and cognitive functions of children.

4.9 Overdose

Symptoms and signs
Acute ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma. ECG changes (small broadening of the QRS-complex and extension of the PR-interval) may occur.

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage or treatment with activated charcoal should be performed if indicated. There is no experience with haemodialysis as treatment for overdose. In 6 patients with renal failure who had been dialysed for 4 hours, 20% of the amount of lamotrigine in the body was removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics
ATC code: N03A X09

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

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

In another 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.

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. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

Distribution
Binding to plasma proteins is about 55 % it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 l/kg.

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

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 substances metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination
The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10 % is excreted unchanged in the urine. Only about 2 % of substance-related material is excreted in
faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.

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

**Special patient groups**

**Children**

Clearance adjusted for bodyweight 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 substances such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see section 4.2).

**Elderly**

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150 mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical 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. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

**Impaired renal function**

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

**Impaired hepatic function**

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, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see section 4.2).

### 5.3 Preclinical safety data

Lamotrigine in dosages above the highest therapeutic maintenance dose does not induce teratogenicity in rats, mice and rabbits. Doses eliciting maternal toxicity reduced fetal weight and retarded skeletal ossification in rats and mice.

In rats, enhanced fetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (days 15-20).

Animal experiments did not reveal impairment of fertility by lamotrigine.

Lamotrigine reduced fetal folate levels in rats. Folate deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Lactose monohydrate
- Cellulose microcrystalline
- Starch pregelatinised maize
- Povidone K-30
- Silica colloidal andryhous
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
Transparent PVC/PVDC-aluminium blisters lidded with aluminium foil

Pack sizes: 21, 30, 42, 56, 60, 90 or 100 tablets.
Calendar packs: 21, 42 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
1 **NAME OF THE MEDICINAL PRODUCT**
Lamotrigine 50 mg tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 50 mg lamotrigine.

Excipient: 36 mg lactose monohydrate/tablet

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Tablet

Lamotrigine 50 mg Tablets are white to off white, round-shaped tablet, debossed with the number “50” on one side and debossed “LT” on the other side of the tablet.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

**Epilepsy**

*Adults and adolescents*

Monotherapy of:
- Partial epilepsy with or without generalisation
- Primary generalised epilepsy

Monotherapy in children under 12 years of age is not recommended.

Add on therapy in epilepsy:
- Partial seizures
- Generalised seizures:
  - primary seizures
  - secondary tonic-clonic seizures
- Seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic agent combinations fail.

*Children over 2 years of age*

Add-on therapy in:
- Partial seizures
- Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fails.

This medicinal product should only be started by a neurologist or paediatric neurologist with experience in the treatment of epilepsy or used in departments of neurology and similar departments.

4.2 **Posology and method of administration**

To achieve the maintenance dose, the weight of a patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine is not equal to whole tablets, the dose to be administered should be that of the lower number of whole tablets.

For doses not realisable/practicable with this medicinal product, other strengths of this medicinal product or other pharmaceutical forms and products are available.

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with lamotrigine, or other AEDs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

**Dosage in monotherapy**

*Adults and adolescents*

The initial lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 mg-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.
Table 1: Recommended dose escalation of lamotrigine for adults and adolescents on monotherapy.

<table>
<thead>
<tr>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks.

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

**Dosage in add-on therapy**

**Adults and adolescents**

In patients taking valproate with / without any other AED the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 – 400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100-200 mg/day given once a day or in two divided doses.

Table 2: Recommended dose escalation of lamotrigine for adults and adolescents on combined therapy.

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>12.5 mg (given as 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>50 mg (once a day)</td>
<td>100 mg (two divided doses)</td>
<td>200-400 mg (two divided doses)</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors See section 4.5</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

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

**Children aged 2 to 12 years**

In patients taking valproate with / without any other AED, the initial lamotrigine dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of
1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses, with a maximum dose of 400 mg/day.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

Table 3: Recommended dose escalation of lamotrigine for children aged 2-12 years on combined therapy (Total daily dose in mg/kg bodyweight/day)

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>0.15 mg/kg ** (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (two divided doses), up to a maximum dose of 400 mg/day</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors</td>
<td>0.3 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or in two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

**NOTE: The recommended dosing schedule for children may not be achievable with the current strengths of the tablets.

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

It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

Adults and children over 2 years of age
(Add-on therapy of Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fail)
See above-mentioned dosing schedules.

Children aged less than 2 years
There is insufficient information on the use of lamotrigine in children aged less than 2 years.

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

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

Renal impairment
Caution should be exercised when administering lamotrigine 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).

**Combination with (continuous) oral hormonal contraceptives**

It is recommended to use continuous contraceptives in patients already taking maintenance doses of lamotrigine and starting oral hormonal contraceptives (see sections 4.4 and 4.5).

The following situations may occur:

(a) **Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

When starting hormonal contraceptives, in most cases the maintenance dose of lamotrigine may need to be increased by as much as two-fold (see sections 4.4 and 4.5). Lamotrigine plasma concentrations should be measured before and after starting hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. Dose escalation should follow the recommended dosing schedule.

(b) **Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

In most cases, the maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual clinical response (see sections 4.4 and 4.5). Adjustment of the dose should also be established in accordance with the individual plasma concentration of lamotrigine and/or the clinical response (the occurrence of dose-related adverse effects). Lamotrigine plasma concentrations should be measured before and after stopping hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. After stopping hormonal contraceptives, it is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg a week over a period of 3 weeks.

(c) **Starting lamotrigine in patients already taking continuous hormonal contraceptives:**

The recommended dosing schedules should be used (see Tables 1 and 2).

**Pregnancy**

See section 4.6.

**Re-starting therapy**

The need for escalation to maintenance dose should be carefully assessed when re-starting lamotrigine in patients who have discontinued it, 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), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy.

**Method of administration**

The tablets should be swallowed whole with a little water, and should be taken as far as possible at the same time every day, on an empty stomach or with a meal.

4.3 **Contraindications**

Lamotrigine is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients.

4.4 **Special warnings and precautions for use**

Due to possible cross-reactions, lamotrigine should be administered with special precaution in individuals with known hypersensitivity to carbamazepine and phenytoin.

The switching of patients between lamotrigine products from different sources is to be avoided without prior consideration by the clinician.

**Skin reactions**

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however, rarely serious potentially life threatening skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).
The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence of children under the age of 12 requiring hospitalisation due to rash is from 1 in 300 to 1 in 100 (see section 4.8).

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a medicinal product reaction 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, which increases the mean half-life of lamotrigine nearly two-fold (See section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not product-related.

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 (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Withdrawal of lamotrigine
Abrupt withdrawal of lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

Potential pharmacokinetic interactions should be taken into consideration in case of any alteration in treatment (e.g. the introduction or withdrawal of other antiepileptic agents, see sections 4.2 and 4.5). Lamotrigine can increase attacks in some patients.

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

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

Use in combination with hormonal contraceptives
Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyloestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold (see section 4.5). A decrease in lamotrigine plasma concentration was associated with loss of control of epileptic attacks. Following dose escalation, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. This has been associated with dose-related unwanted effects. 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 (e.g. ‘pill-free week’), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). These increases will be greater when lamotrigine dose increases are made in the days before or during the
week of inactive treatment. After starting the hormonal contraceptive treatment again the lamotrigine levels will decrease. Variations in lamotrigine levels of this order are not recommended.

Therefore, although it has not been evaluated whether these increases or decreases in lamotrigine levels can lead to the occurrence of dose-related undesirable effects or a loss of control of epileptic attacks, respectively, it is recommended that patients on maintenance doses of lamotrigine and starting hormonal contraceptives use a continuous hormonal contraceptive and not those that include a week of inactive medicinal product.

Other hormonal contraceptive and hormone replacement therapy (HRT) treatments 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 follicle-stimulating hormone (FSH) and luteinising hormone (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, e.g. breakthrough bleeding.

**Renal impairment**
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.

**Hepatic impairment**
In patients with moderate (Child-Pugh grade B) and severe (Child-Pugh grade C) hepatic impairment it has been shown that initial, escalation and maintenance doses should be reduced (see section 4.2). Caution should be exercised when dosing this hepatically impaired population.

**Women of childbearing age**
Women of childbearing age and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations may be enhanced in combination therapy with other anticonvulsants.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

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 substance-metabolising enzymes, and interactions between lamotrigine and substances metabolised by cytochrome P450 (CYP) enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

**Effect of lamotrigine on the pharmacokinetics of other active substances**

**Antiepileptics**
There have been reports of central nervous system events including headache, nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

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 antiepileptic drugs from protein binding sites.
Hormonal contraceptives
Effect of lamotrigine on hormonal contraceptives:
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 hormonal contraceptive pill. A modest increase in overall clearance of the levonorgestrel component was observed. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. 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.

Effect of other active substances on the pharmacokinetics of lamotrigine
Antiepileptic agents which induce substance-metabolising enzymes in the liver (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). The half-life of lamotrigine is shortened to approximately 14 hours; in children below 12 years, approximately 7 hours.

Sodium valproate, which competes with lamotrigine for hepatic substance-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two fold. The half-life of lamotrigine is extended to approx. 70 hours; in children below 12 years, 45-55 hours.

Table 4: Effects of other active substances on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Active substances that significantly inhibit glucuronidation of lamotrigine</th>
<th>Active substances that significantly induce glucuronidation of lamotrigine</th>
<th>Active substances that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Primidone</td>
<td>Primidone</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Ethinyloestradiol/levonorgestrel combination*</td>
<td>Ethinyloestradiol/levonorgestrel combination*</td>
<td>Oxcarbazepine**</td>
</tr>
</tbody>
</table>

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

** In a study in healthy adult volunteers using doses of 200 mg/day lamotrigine and 1200 mg/day oxcarbazepine, results showed that compared with placebo, the mean values for steady state peak plasma concentration (C_max) and area under the curve (AUC_0-24) of lamotrigine were reduced by 2% and 8%, respectively. The 90% confidence intervals indicated that the differences were between -22% and +8% for AUC_0-24 and -15% and +15% for C_max. Adverse events were reported more frequently with oxcarbazepine and lamotrigine than with either monotherapy. The most common undesirable effects were headache, dizziness, nausea and somnolence.

*** In a study in 10 healthy adult males, rifampicin increased the clearance and shortened the half-life of lamotrigine.

Hormonal contraceptives
Effect of hormonal contraceptives on lamotrigine:
In a study of 16 female volunteers, 30 mcg ethinyloestradiol/150 mcg levonorgestrel in a combined hormonal contraceptive pill caused an approximately two-fold increase in lamotrigine overall clearance, resulting in an average 52% and 39% reduction in lamotrigine area under the curve (AUC) and C_max, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive treatment (e.g. "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.

If the therapeutic effect of lamotrigine is uncertain although dose adjustments have been made, a non-hormonal contraceptive method could be considered.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during lamotrigine therapy.

Psychoactive medicines
The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine.
In a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C\text{max} of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of 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.

\textit{In vitro} inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-\textit{N}-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of active substances eliminated predominantly by CYP2D6. Results of \textit{in vitro} experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. However, it has been reported that sertraline may increase the toxicity of lamotrigine by increasing the plasma concentration of lamotrigine.

\textit{Folic acid}

Interaction with folic acid metabolism (see sections 4.4 and 4.6).

During prolonged human lamotrigine dosing, there were no significant changes in haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folic acid concentrations up to 1 year or red blood cell folic acid concentration up to 5 years.

4.6 Pregnancy and lactation

\textbf{Pregnancy}

\textit{Risk related to epilepsy and antiepileptic agents in general}

It is known that newborn children from mothers who use antiepileptic products or suffer from epilepsy more frequently have development disorders, such as cardiac abnormalities and cranial facial disorders, than other babies. Multiple antiepileptic therapy during pregnancy may increase the risk of fetal malformations and should therefore be avoided, unless it appears justified after having assessed the risk-benefit ratio.

\textit{Risk linked to lamotrigine}

There are limited data available on the use of lamotrigine during pregnancy. Lamotrigine passes through the placenta, since plasma concentrations in some newborns were at therapeutic levels. Lamotrigine should not be used in pregnancy, unless the potential benefits of treatment to the mother outweigh any possible risks to the developing fetus. Reduction or discontinuation of seizure prophylaxis may carry considerable risk for both mother and fetus that is probably greater than any risk of malformation.

Animal experiments have shown no evidence of teratogenic effects (see section 5.3).

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

Furthermore, it is important that pregnant women and women of child-bearing potential practice monotherapy whenever possible.

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

Lamotrigine plasma levels should therefore be monitored before, during and after pregnancy, as well as during birth. If necessary, the dose should be adapted, to maintain the lamotrigine plasma concentration on the same level as before pregnancy. In addition, dose-related adverse effects should be monitored after birth.
**Lactation**
Lamotrigine is excreted into breast milk and may reach serum concentrations in the breast-fed infant that are in the usual therapeutic range in the mother. Mothers should therefore breast-feed only after a careful risk-benefit assessment for the infant. If the infant is breast-fed, he/she should be monitored for possible effects.

**4.7 Effects on ability to drive and use machines**
Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo.

In clinical trials with lamotrigine adverse effects of a neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all AED therapy patients should consult their physician on the specific issues of driving and epilepsy.

**4.8 Undesirable effects**
The following convention has been utilised for the classification of undesirable effects:
Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1000 and <1/100)
Rare (≥1/10,000 and <1/1000)
Very rare (≤1/10,000, including isolated reports)

<table>
<thead>
<tr>
<th>Table 5: Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>Immune system disorders</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Eye disorders</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
</tr>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Skin rash</td>
</tr>
<tr>
<td><strong>Musculoskeletal, connective tissue and bone disorders</strong></td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
</tr>
</tbody>
</table>

1 In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4).

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

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence in children under the age of 12 requiring hospitalisation due to rash ranges from 1 in 300 to 1 in 100 (see section 4.4).

In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a reaction 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).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related.

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 (DIC) and multorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

2 Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis) may or may not be associated with the hypersensitivity syndrome.

3 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.

There are insufficient data available about the effect of lamotrigine on growth, development and cognitive functions of children.
4.9 Overdose

Symptoms and signs
Acute ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma. ECG changes (small broadening of the QRS-complex and extension of the PR-interval) may occur.

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage or treatment with activated charcoal should be performed if indicated. There is no experience with haemodialysis as treatment for overdose. In 6 patients with renal failure who had been dialysed for 4 hours, 20% of the amount of lamotrigine in the body was removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antiepileptics
ATC code: N03A X09

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

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

In another 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.

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. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

Distribution
Binding to plasma proteins is about 55 % it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 l/kg.

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

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 substances metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination
The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10 % is excreted unchanged in the urine. Only about 2 % of substance-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.
The half-life of lamotrigine is greatly affected by concomitant treatment. Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing substances such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with sodium valproate alone. (see section 4.2).

**Special patient groups**

**Children**

Clearance adjusted for bodyweight 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 substances such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see section 4.2).

**Elderly**

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150 mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical 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. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

**Impaired renal function**

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

**Impaired hepatic function**

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, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Lamotrigine in dosages above the highest therapeutic maintenance dose does not induce teratogenicity in rats, mice and rabbits. Doses eliciting maternal toxicity reduced fetal weight and retarded skeletal ossification in rats and mice.

In rats, enhanced fetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (days 15-20).

Animal experiments did not reveal impairment of fertility by lamotrigine.

Lamotrigine reduced fetal folate levels in rats. Folate deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Cellulose microcrystalline
- Starch pregelatinised maize
- Povidone K-30
- Silica colloidal andryhous
- Sodium starch glycolate (Type A)
- Magnesium stearate
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
Transparent PVC/PVDC-aluminium blisters lidded with aluminium foil

Pack sizes: 21, 30, 42, 56, 60, 90 or 100 tablets.
Calendar packs: 21, 42 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Eastbourne,
BN22 9AG,
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0501

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
10th June 2005

10 DATE OF REVISION OF THE TEXT
27/06/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg lamotrigine.

Excipient: 71.96 mg lactose monohydrate/tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Lamotrigine 100 mg Tablets are peach, diamond-shaped tablet, debossed with the number “93” on one side and scored between the two numbers, debossed “463” on the other side of the tablet.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy
Adults and adolescents
Monotherapy of:
- Partial epilepsy with or without generalisation
- Primary generalised epilepsy

Monotherapy in children under 12 years of age is not recommended.

Add on therapy in epilepsy:
- Partial seizures
- Generalised seizures:
  - primary seizures
  - secondary tonic-clonic seizures
- Seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic agent combinations fail.

Children over 2 years of age
Add-on therapy in:
- Partial seizures
- Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fails.

This medicinal product should only be started by a neurologist or paediatric neurologist with experience in the treatment of epilepsy or used in departments of neurology and similar departments.

4.2 Posology and method of administration
To achieve the maintenance dose, the weight of a patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine is not equal to whole tablets, the dose to be administered should be that of the lower number of whole tablets.

For doses not realisable/practicable with this medicinal product, other strengths of this medicinal product or other pharmaceutical forms and products are available.

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with lamotrigine, or other AEDs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

**Dosage in monotherapy**
Adults and adolescents
The initial lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 mg-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.
Table 1: Recommended dose escalation of lamotrigine for adults and adolescents on monotherapy.

<table>
<thead>
<tr>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks.

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

Dosage in add-on therapy

Adults and adolescents

In patients taking valproate with / without any other AED the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 – 400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100-200 mg/day given once a day or in two divided doses.

Table 2: Recommended dose escalation of lamotrigine for adults and adolescents on combined therapy.

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>12.5 mg (given as 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>50 mg (once a day)</td>
<td>100 mg (two divided doses)</td>
<td>200-400 mg (two divided doses)</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors See section 4.5</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

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

Children aged 2 to 12 years

In patients taking valproate with / without any other AED, the initial lamotrigine dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks,
followed by 1.2 mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of
1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to
achieve optimal response is 5-15 mg/kg/day given in two divided doses, with a maximum dose of 400
mg/day.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine
glucuronidation, the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two
divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for
two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1-2 weeks until
the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10
mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

Table 3: Recommended dose escalation of lamotrigine for children aged 2-12 years on combined
therapy (Total daily dose in mg/kg bodyweight/day)

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>0.15 mg/kg ** (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (two divided doses), up to a maximum dose of 400 mg/day</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors</td>
<td>0.3 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or in two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not
known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used,
thereafter, the dose should be increased until optimal response is achieved.

**NOTE: The recommended dosing schedule for children may not be achievable with the current
strengths of the tablets.
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash
(see section 4.4).
It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the
recommended range.

Adults and children over 2 years of age
(Add-on therapy of Lennox-Gastaut syndrome if treatment with other available combinations of anti-
epileptic agents fail)
See above-mentioned dosing schedules.

Children aged less than 2 years
There is insufficient information on the use of lamotrigine in children aged less than 2 years.

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

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

Renal impairment
Caution should be exercised when administering lamotrigine 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).

**Combination with (continuous) oral hormonal contraceptives**

It is recommended to use continuous contraceptives in patients already taking maintenance doses of lamotrigine and starting oral hormonal contraceptives (see sections 4.4. and 4.5).

The following situations may occur:

(a) **Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

When starting hormonal contraceptives, in most cases the maintenance dose of lamotrigine may need to be increased by as much as two-fold (see sections 4.4 and 4.5). Lamotrigine plasma concentrations should be measured before and after starting hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. Dose escalation should follow the recommended dosing schedule.

(b) **Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

In most cases, the maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual clinical response (see sections 4.4 and 4.5). Adjustment of the dose should also be established in accordance with the individual plasma concentration of lamotrigine and/or the clinical response (the occurrence of dose-related adverse effects). Lamotrigine plasma concentrations should be measured before and after stopping hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. After stopping hormonal contraceptives, it is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg a week over a period of 3 weeks.

(c) **Starting lamotrigine in patients already taking continuous hormonal contraceptives:**

The recommended dosing schedules should be used (see Tables 1 and 2).

**Pregnancy**

See section 4.6.

**Re-starting therapy**

The need for escalation to maintenance dose should be carefully assessed when re-starting lamotrigine in patients who have discontinued it, 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), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy.

**Method of administration**

The tablets should be swallowed whole with a little water, and should be taken as far as possible at the same time every day, on an empty stomach or with a meal.

**4.3 Contraindications**

Lamotrigine is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients.

**4.4 Special warnings and precautions for use**

Due to possible cross-reactions, lamotrigine should be administered with special precaution in individuals with known hypersensitivity to carbamazepine and phenytoin.

The switching of patients between lamotrigine products from different sources is to be avoided without prior consideration by the clinician.

**Skin reactions**

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however, rarely serious potentially life threatening skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).
The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence of children under the age of 12 requiring hospitalisation due to rash is from 1 in 300 to 1 in 100 (see section 4.8).

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a medicinal product reaction 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, which increases the mean half-life of lamotrigine nearly two-fold (See section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not product-related.

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 (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Withdrawal of lamotrigine
Abrupt withdrawal of lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

Potential pharmacokinetic interactions should be taken into consideration in case of any alteration in treatment (e.g. the introduction or withdrawal of other antiepileptic agents, see sections 4.2 and 4.5). Lamotrigine can increase attacks in some patients.

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

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

Use in combination with hormonal contraceptives
Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyloestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold (see section 4.5). A decrease in lamotrigine plasma concentration was associated with loss of control of epileptic attacks. Following dose escalation, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. This has been associated with dose-related unwanted effects. 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 (e.g. ‘pill-free week’), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). These increases will be greater when lamotrigine dose increases are made in the days before or during the
week of inactive treatment. After starting the hormonal contraceptive treatment again the lamotrigine levels will decrease. Variations in lamotrigine levels of this order are not recommended.

Therefore, although it has not been evaluated whether these increases or decreases in lamotrigine levels can lead to the occurrence of dose-related undesirable effects or a loss of control of epileptic attacks, respectively, it is recommended that patients on maintenance doses of lamotrigine and starting hormonal contraceptives use a continuous hormonal contraceptive and not those that include a week of inactive medicinal product.

Other hormonal contraceptive and hormone replacement therapy (HRT) treatments 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 follicle-stimulating hormone (FSH) and luteinising hormone (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, e.g. breakthrough bleeding.

**Renal impairment**
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.

**Hepatic impairment**
In patients with moderate (Child-Pugh grade B) and severe (Child-Pugh grade C) hepatic impairment it has been shown that initial, escalation and maintenance doses should be reduced (see section 4.2). Caution should be exercised when dosing this hepatically impaired population.

**Women of childbearing age**
Women of childbearing age and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations may be enhanced in combination therapy with other anticonvulsants.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 **Interaction with other medicinal products and other forms of interaction**
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 substance-metabolising enzymes, and interactions between lamotrigine and substances metabolised by cytochrome P450 (CYP) enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

**Effect of lamotrigine on the pharmacokinetics of other active substances**

*Antiepileptics*
There have been reports of central nervous system events including headache, nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

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 antiepileptic drugs from protein binding sites.
**Hormonal contraceptives**

**Effect of lamotrigine on hormonal contraceptives:**
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 hormonal contraceptive pill. A modest increase in overall clearance of the levonorgestrel component was observed. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. 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.

**Effect of other active substances on the pharmacokinetics of lamotrigine**
Antiepileptic agents which induce substance-metabolising enzymes in the liver (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). The half-life of lamotrigine is shortened to approximately 14 hours; in children below 12 years, approximately 7 hours.

Sodium valproate, which competes with lamotrigine for hepatic substance-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two fold. The half-life of lamotrigine is extended to approx. 70 hours; in children below 12 years, 45-55 hours.

<table>
<thead>
<tr>
<th>Active substances that significantly inhibit glucuronidation of lamotrigine</th>
<th>Active substances that significantly induce glucuronidation of lamotrigine</th>
<th>Active substances that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Oxcarbazepine**</td>
</tr>
<tr>
<td></td>
<td>Rifampicin***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethinyloestradiol/levonorgestrel combination*</td>
<td></td>
</tr>
</tbody>
</table>

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

** In a study in healthy adult volunteers using doses of 200 mg/day lamotrigine and 1200 mg/day oxcarbazepine, results showed that compared with placebo, the mean values for steady state peak plasma concentration (C_max) and area under the curve (AUC_0-24) of lamotrigine were reduced by 2% and 8%, respectively. The 90% confidence intervals indicated that the differences were between -22% and +8% for AUC_0-24 and -15% and +15% for C_max. Adverse events were reported more frequently with oxcarbazepine and lamotrigine than with either monotherapy. The most common undesirable effects were headache, dizziness, nausea and somnolence.

*** In a study in 10 healthy adult males, rifampicin increased the clearance and shortened the half-life of lamotrigine.

**Hormonal contraceptives**

**Effect of hormonal contraceptives on lamotrigine:**
In a study of 16 female volunteers, 30 mcg ethinyloestradiol/150 mcg levonorgestrel in a combined hormonal contraceptive pill caused an approximately two-fold increase in lamotrigine overall clearance, resulting in an average 52% and 39% reduction in lamotrigine area under the curve (AUC) and C_max, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive treatment (e.g. "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.

If the therapeutic effect of lamotrigine is uncertain although dose adjustments have been made, a non-hormonal contraceptive method could be considered.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during lamotrigine therapy.

**Psychoactive medicines**
The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine.
In a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C<sub>max</sub> 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 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 vitro* inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of active substances eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. However it has been reported that sertraline may increase the toxicity of lamotrigine by increasing the plasma concentration of lamotrigine.

**Folic acid**

Interaction with folic acid metabolism (see sections 4.4 and 4.6).

During prolonged human lamotrigine dosing, there were no significant changes in haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folic acid concentrations up to 1 year or red blood cell folic acid concentration up to 5 years.

### 4.6 Pregnancy and lactation

#### Pregnancy

**Risk related to epilepsy and antiepileptic agents in general**

It is known that newborn children from mothers who use antiepileptic products or suffer from epilepsy more frequently have development disorders, such as cardiac abnormalities and cranial facial disorders, than other babies. Multiple antiepileptic therapy during pregnancy may increase the risk of fetal malformations and should therefore be avoided, unless it appears justified after having assessed the risk-benefit ratio.

**Risk linked to lamotrigine**

There are limited data available on the use of lamotrigine during pregnancy. Lamotrigine passes through the placenta, since plasma concentrations in some newborns were at therapeutic levels. Lamotrigine should not be used in pregnancy, unless the potential benefits of treatment to the mother outweigh any possible risks to the developing fetus. Reduction or discontinuation of seizure prophylaxis may carry considerable risk for both mother and fetus that is probably greater than any risk of malformation.

Animal experiments have shown no evidence of teratogenic effects (see section 5.3).

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

Furthermore, it is important that pregnant women and women of child-bearing potential practice monotherapy whenever possible.

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

Lamotrigine plasma levels should therefore be monitored before, during and after pregnancy, as well as during birth. If necessary, the dose should be adapted, to maintain the lamotrigine plasma concentration on the same level as before pregnancy. In addition, dose-related adverse effects should be monitored after birth.

#### Lactation

Lamotrigine is excreted into breast milk and may reach serum concentrations in the breast-fed infant that are in the usual therapeutic range in the mother. Mothers should therefore breast-feed only after a...
careful risk-benefit assessment for the infant. If the infant is breast-fed, he/she should be monitored for possible effects.

4.7 Effects on ability to drive and use machines

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo.

In clinical trials with lamotrigine adverse effects of a neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all AED therapy patients should consult their physician on the specific issues of driving and epilepsy.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Haematological abnormalities^2</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity syndrome</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Irritability</td>
<td>Aggression</td>
<td></td>
<td>Tics, hallucinations, confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Drowsiness, insomnia, tremor, nystagmus, ataxia</td>
<td></td>
<td>Agitation, unsteadiness, movement disorders, worsening of Parkinson’s disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency^3</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, blurred vision</td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disturbance, nausea, vomiting, diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Increased liver function tests, hepatic dysfunction, hepatic failure^4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin rash^1</td>
<td></td>
<td>Stevens Johnson syndrome</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Musculoskeletal, connective tissue and bone disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Lupus-like reactions</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Tiredness</td>
</tr>
</tbody>
</table>

1In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4).

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

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence in children under the age of 12 requiring hospitalisation due to rash ranges from 1 in 300 to 1 in 100 (see section 4.4).

In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a reaction 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).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related.

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 (DIC) and multorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis) may or may not be associated with the hypersensitivity syndrome.

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.

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

There are insufficient data available about the effect of lamotrigine on growth, development and cognitive functions of children.

### 4.9 Overdose

#### Symptoms and signs

Acute ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma. ECG changes (small broadening of the QRS-complex and extension of the PR-interval) may occur.
Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage or treatment with activated charcoal should be performed if indicated. There is no experience with haemodialysis as treatment for overdose. In 6 patients with renal failure who had been dialysed for 4 hours, 20% of the amount of lamotrigine in the body was removed.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antiepileptics
ATC code: N03A X09
Mode of action
The results of pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage-gated sodium channels. It produces a use- and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

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

In another study, single oral doses of 600 mg carbamazepine significantly impaired fine visual motor coordination 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.

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. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable interindividual variation in steady state maximum concentrations but within an individual concentrations vary very little.

Distribution
Binding to plasma proteins is about 55 % it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 l/kg.

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

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 substances metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination
The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10 % is excreted unchanged in the urine. Only about 2 % of substance-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.

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

Children
Clearance adjusted for bodyweight 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 substances such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see section 4.2).

Elderly
The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150 mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical 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. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

Impaired renal function
There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

Impaired hepatic function
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, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see section 4.2).

5.3 Preclinical safety data
Lamotrigine in dosages above the highest therapeutic maintenance dose does not induce teratogenicity in rats, mice and rabbits. Doses eliciting maternal toxicity reduced fetal weight and retarded skeletal ossification in rats and mice.

In rats, enhanced fetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (days 15-20).

Animal experiments did not reveal impairment of fertility by lamotrigine.

Lamotrigine reduced fetal folate levels in rats. Folate deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Cellulose microcrystalline
Starch pregelatinised maize
Povidone K-30
Silica colloidal anhydrous
Sodium starch glycolate (Type A)
Magnesium stearate
Yellow orange S (E110)

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
3 years

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

6.5 Nature and contents of container
Transparent PVC/PVDC-aluminium blisters lidded with aluminium foil

Pack sizes: 21, 30, 42, 56, 60, 90 or 100 tablets.
Calendar packs: 21, 42 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Eastbourne,
BN22 9AG,
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0502

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
10th June 2005

10 DATE OF REVISION OF THE TEXT
27/06/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 200 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg lamotrigine.

Excipient: 143.31 mg lactose monohydrate/tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Lamotrigine 200 mg Tablets are blue, diamond-shaped tablet, debossed with the number “93” on one side and scored between the two numbers, debossed “7248” on the other side of the tablet.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy
  Adults and adolescents
  Monotherapy of:
  - Partial epilepsy with or without generalisation
  - Primary generalised epilepsy

Monotherapy in children under 12 years of age is not recommended.

Add on therapy in epilepsy:
  - Partial seizures
  - Generalised seizures:
    - primary seizures
    - secondary tonic-clonic seizures
  - Seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic agent combinations fail.

Children over 2 years of age
Add-on therapy in:
  - Partial seizures
  - Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fails.

This medicinal product should only be started by a neurologist or paediatric neurologist with experience in the treatment of epilepsy or used in departments of neurology and similar departments.

4.2 Posology and method of administration
To achieve the maintenance dose, the weight of a patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine is not equal to whole tablets, the dose to be administered should be that of the lower number of whole tablets.

For doses not realisable/practicable with this medicinal product, other strengths of this medicinal product or other pharmaceutical forms and products are available.

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with lamotrigine, or other AEDs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

Dosage in monotherapy
  Adults and adolescents
The initial lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 mg-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.
Table 1: Recommended dose escalation of lamotrigine for adults and adolescents on monotherapy.

<table>
<thead>
<tr>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks</td>
</tr>
</tbody>
</table>

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

**Dosage in add-on therapy**

**Adults and adolescents**

In patients taking valproate with / without any other AED the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 – 400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100-200 mg/day given once a day or in two divided doses.

**Table 2: Recommended dose escalation of lamotrigine for adults and adolescents on combined therapy.**

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>12.5 mg (given as 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 25-50 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>50 mg (once a day)</td>
<td>100 mg (two divided doses)</td>
<td>200-400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors See section 4.5</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100-200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50-100 mg every 1-2 weeks</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

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

**Children aged 2 to 12 years**

In patients taking valproate with / without any other AED, the initial lamotrigine dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

In those patients taking enzyme inducing AEDs with / without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks,
followed by 1.2 mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses, with a maximum dose of 400 mg/day.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

Table 3: Recommended dose escalation of lamotrigine for children aged 2-12 years on combined therapy (Total daily dose in mg/kg bodyweight/day)

<table>
<thead>
<tr>
<th>Concomitant treatment</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate with / without any other AEDs</td>
<td>0.15 mg/kg ** (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
<tr>
<td>Enzyme inducing AEDs* with / without other AEDs (except valproate)</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (two divided doses), up to a maximum dose of 400 mg/day</td>
</tr>
<tr>
<td>Oxcarbazepine without other enzyme inducers or inhibitors</td>
<td>0.3 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg (once a day or in two divided doses)</td>
<td>0.6 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-10 mg/kg (once a day or in two divided doses), up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

*eg phenytoin, carbamazepine, phenobarbital and primidone

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

**NOTE: The recommended dosing schedule for children may not be achievable with the current strengths of the tablets.

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

It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

Adults and children over 2 years of age
(Add-on therapy of Lennox-Gastaut syndrome if treatment with other available combinations of antiepileptic agents fail)
See above-mentioned dosing schedules.

Children aged less than 2 years
There is insufficient information on the use of lamotrigine in children aged less than 2 years.

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

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

Renal impairment
Caution should be exercised when administering lamotrigine 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).

**Combination with (continuous) oral hormonal contraceptives**

It is recommended to use continuous contraceptives in patients already taking maintenance doses of lamotrigine and starting oral hormonal contraceptives (see sections 4.4 and 4.5).

The following situations may occur:

(a) **Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

When starting hormonal contraceptives, in most cases the maintenance dose of lamotrigine may need to be increased by as much as two-fold (see sections 4.4 and 4.5). Lamotrigine plasma concentrations should be measured before and after starting hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. Dose escalation should follow the recommended dosing schedule.

(b) **Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and not taking additional inducers of lamotrigine glucuronidation:**

In most cases, the maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual clinical response (see sections 4.4 and 4.5). Adjustment of the dose should also be established in accordance with the individual plasma concentration of lamotrigine and/or the clinical response (the occurrence of dose-related adverse effects). Lamotrigine plasma concentrations should be measured before and after stopping hormonal contraceptives to maintain the baseline concentration of lamotrigine. If necessary, the dose should be adapted. After stopping hormonal contraceptives, it is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg a week over a period of 3 weeks.

(c) **Starting lamotrigine in patients already taking continuous hormonal contraceptives:**

The recommended dosing schedules should be used (see Tables 1 and 2).

**Pregnancy**

See section 4.6.

**Re-starting therapy**

The need for escalation to maintenance dose should be carefully assessed when re-starting lamotrigine in patients who have discontinued it, 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), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy.

**Method of administration**

The tablets should be swallowed whole with a little water, and should be taken as far as possible at the same time every day, on an empty stomach or with a meal.

**4.3 Contraindications**

Lamotrigine is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients.

**4.4 Special warnings and precautions for use**

Due to possible cross-reactions, lamotrigine should be administered with special precaution in individuals with known hypersensitivity to carbamazepine and phenytoin.

The switching of patients between lamotrigine products from different sources is to be avoided without prior consideration by the clinician.

**Skin reactions**

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however, rarely serious potentially life threatening skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).
The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence of children under the age of 12 requiring hospitalisation due to rash is from 1 in 300 to 1 in 100 (see section 4.8).

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a medicinal product reaction 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, which increases the mean half-life of lamotrigine nearly two-fold (See section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not product-related.

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 (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Withdrawal of lamotrigine
Abrupt withdrawal of lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of 2 weeks.

Potential pharmacokinetic interactions should be taken into consideration in case of any alteration in treatment (e.g. the introduction or withdrawal of other antiepileptic agents, see sections 4.2 and 4.5). Lamotrigine can increase attacks in some patients.

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

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

Use in combination with hormonal contraceptives
Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyl oestradiol/levonorgestrel (30 mcg/150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold (see section 4.5). A decrease in lamotrigine plasma concentration was associated with loss of control of epileptic attacks. Following dose escalation, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. This has been associated with dose-related unwanted effects. 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 (e.g. ‘pill-free week’), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). These increases will be greater when lamotrigine dose increases are made in the days before or during the
week of inactive treatment. After starting the hormonal contraceptive treatment again the lamotrigine levels will decrease. Variations in lamotrigine levels of this order are not recommended.

Therefore, although it has not been evaluated whether these increases or decreases in lamotrigine levels can lead to the occurrence of dose-related undesirable effects or a loss of control of epileptic attacks, respectively, it is recommended that patients on maintenance doses of lamotrigine and starting hormonal contraceptives use a continuous hormonal contraceptive and not those that include a week of inactive medicinal product.

Other hormonal contraceptive and hormone replacement therapy (HRT) treatments 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 follicle-stimulating hormone (FSH) and luteinising hormone (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, e.g. breakthrough bleeding.

**Renal impairment**
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.

**Hepatic impairment**
In patients with moderate (Child-Pugh grade B) and severe (Child-Pugh grade C) hepatic impairment it has been shown that initial, escalation and maintenance doses should be reduced (see section 4.2). Caution should be exercised when dosing this hepatically impaired population.

**Women of childbearing age**
Women of childbearing age and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations may be enhanced in combination therapy with other anticonvulsants.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains yellow orange S (E110) and may cause allergic-like reactions including asthma. Such reactions are more common in patients with hypersensitivity to acetylsalicylic acid.

### 4.5 Interaction with other medicinal products and other forms of interaction

**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 substance-metabolising enzymes, and interactions between lamotrigine and substances metabolised by cytochrome P450 (CYP) enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

**Effect of lamotrigine on the pharmacokinetics of other active substances**

**Antiepileptics**
There have been reports of central nervous system events including headache, nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced.

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 antiepileptic drugs from protein binding sites.
Hormonal contraceptives

Effect of lamotrigine on hormonal contraceptives:
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 hormonal contraceptive pill. A modest increase in overall clearance of the levonorgestrel component was observed. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. 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.

Effect of other active substances on the pharmacokinetics of lamotrigine
Antiepileptic agents which induce substance-metabolising enzymes in the liver (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). The half-life of lamotrigine is shortened to approximately 14 hours; in children below 12 years, approximately 7 hours.

Sodium valproate, which competes with lamotrigine for hepatic substance-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two fold. The half-life of lamotrigine is extended to approx. 70 hours; in children below 12 years, 45-55 hours.

Table 4: Effects of other active substances on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Active substances that significantly inhibit glucuronidation of lamotrigine</th>
<th>Active substances that significantly induce glucuronidation of lamotrigine</th>
<th>Active substances that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Oxcarbazepine**</td>
</tr>
<tr>
<td></td>
<td>Rifampicin***</td>
<td></td>
</tr>
</tbody>
</table>

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

** In a study in healthy adult volunteers using doses of 200 mg/day lamotrigine and 1200 mg/day oxcarbazepine, results showed that compared with placebo, the mean values for steady state peak plasma concentration (C_{max}) and area under the curve (AUC_{0-24}) of lamotrigine were reduced by 2% and 8%, respectively. The 90% confidence intervals indicated that the differences were between -22% and +8% for AUC_{0-24} and -15% and +15% for C_{max}. Adverse events were reported more frequently with oxcarbazepine and lamotrigine than with either monotherapy. The most common undesirable effects were headache, dizziness, nausea and somnolence.

*** In a study in 10 healthy adult males, rifampicin increased the clearance and shortened the half-life of lamotrigine.

Hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine:
In a study of 16 female volunteers, 30 mcg ethinyloestradiol/150 mcg levonorgestrel in a combined hormonal contraceptive pill caused an approximately two-fold increase in lamotrigine overall clearance, resulting in an average 52% and 39% reduction in lamotrigine area under the curve (AUC) and C_{max}, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive treatment (e.g. "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.

If the therapeutic effect of lamotrigine is uncertain although dose adjustments have been made, a non-hormonal contraceptive method could be considered.

Clinicians should exercise appropriate clinical management of women starting or stopping-hormonal contraceptives during lamotrigine therapy.
**Psychoactive medicines**

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

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

Multiple oral doses of 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 vitro* inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-\text{N}-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of active substances eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. However it has been reported that sertraline may increase the toxicity of lamotrigine by increasing the plasma concentration of lamotrigine.

**Folic acid**

Interaction with folic acid metabolism (see sections 4.4 and 4.6).

During prolonged human lamotrigine dosing, there were no significant changes in haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folic acid concentrations up to 1 year or red blood cell folic acid concentration up to 5 years.

**4.6 Pregnancy and lactation**

**Pregnancy**

*Risk related to epilepsy and antiepileptic agents in general*

It is known that newborn children from mothers who use antiepileptic products or suffer from epilepsy more frequently have development disorders, such as cardiac abnormalities and cranial facial disorders, than other babies. Multiple antiepileptic therapy during pregnancy may increase the risk of fetal malformations and should therefore be avoided, unless it appears justified after having assessed the risk-benefit ratio.

*Risk linked to lamotrigine*

There are limited data available on the use of lamotrigine during pregnancy. Lamotrigine passes through the placenta, since plasma concentrations in some newborns were at therapeutic levels. Lamotrigine should not be used in pregnancy, unless the potential benefits of treatment to the mother outweigh any possible risks to the developing fetus. Reduction or discontinuation of seizure prophylaxis may carry considerable risk for both mother and fetus that is probably greater than any risk of malformation.

Animal experiments have shown no evidence of teratogenic effects (see section 5.3).

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

Furthermore, it is important that pregnant women and women of child-bearing potential practice monotherapy whenever possible.

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

Lamotrigine plasma levels should therefore be monitored before, during and after pregnancy, as well as during birth. If necessary, the dose should be adapted, to maintain the lamotrigine plasma concentration on the same level as before pregnancy. In addition, dose-related adverse effects should be monitored after birth.
**Lactation**

Lamotrigine is excreted into breast milk and may reach serum concentrations in the breast-fed infant that are in the usual therapeutic range in the mother. Mothers should therefore breast-feed only after a careful risk-benefit assessment for the infant. If the infant is breast-fed, he/she should be monitored for possible effects.

**4.7 Effects on ability to drive and use machines**

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo.

In clinical trials with lamotrigine adverse effects of a neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all AED therapy patients should consult their physician on the specific issues of driving and epilepsy.

**4.8 Undesirable effects**

The following convention has been utilised for the classification of undesirable effects:

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Haematological abnormalities²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Irritability, Aggression, Tics, hallucinations, confusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness, Drowsiness, insomnia, tremor, nystagmus, ataxia, Agitation, unsteadiness, movement disorders, worsening of Parkinson’s disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, blurred vision, Conjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disturbance, nausea, vomiting, diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Increased liver function tests, hepatic dysfunction, hepatic failure⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td>Stevens Johnson syndrome</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Skin rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Musculoskeletal, connective tissue and bone disorders**

| | | | Lupus-like reactions |
| | | | |

**General disorders**

| | Tiredness |
| | |

1 In double-blind, add-on clinical trials, skin rashes occurred in up to 10% of patients taking lamotrigine and in 5% of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4).

Rarely, serious potentially life-Threatening skin rashes, including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell Syndrome) have been reported. Although the majority recover on withdrawal of the substance, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence in children under the age of 12 requiring hospitalisation due to rash ranges from 1 in 300 to 1 in 100 (see section 4.4).

In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a reaction 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).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related.

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 (DIC) and multorgan failure. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

2 Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis) may or may not be associated with the hypersensitivity syndrome.

3 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.

There are insufficient data available about the effect of lamotrigine on growth, development and cognitive functions of children.
4.9 Overdose

Symptoms and signs
Acute ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma. ECG changes (small broadening of the QRS-complex and extension of the PR-interval) may occur.

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage or treatment with activated charcoal should be performed if indicated. There is no experience with haemodialysis as treatment for overdose. In 6 patients with renal failure who had been dialysed for 4 hours, 20% of the amount of lamotrigine in the body was removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics
ATC code: N03AX09

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

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

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. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

Distribution
Binding to plasma proteins is about 55% it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 l/kg.

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

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 substances metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination
The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of substance-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.
The half-life of lamotrigine is greatly affected by concomitant treatment. Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing substances such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with sodium valproate alone. (see section 4.2).

Special patient groups

Children
Clearance adjusted for bodyweight 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 substances such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see section 4.2).

Elderly
The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150 mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical 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. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

Impaired renal function
There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

Impaired hepatic function
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, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see section 4.2).

5.3 Preclinical safety data
Lamotrigine in dosages above the highest therapeutic maintenance dose does not induce teratogenicity in rats, mice and rabbits. Doses eliciting maternal toxicity reduced fetal weight and retarded skeletal ossification in rats and mice.

In rats, enhanced fetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (days 15-20).

Animal experiments did not reveal impairment of fertility by lamotrigine.

Lamotrigine reduced fetal folate levels in rats. Folate deficiency is assumed to be associated with an enhanced risk of congenital malformations in animals as well as in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose microcrystalline
Starch pregelatinised maize
Povidone K-30
Silica colloidal andryhous
Sodium starch glycolate (Type A)
Magnesium stearate
Indigo carmine (E132)
6.2   **Incompatibilities**
Not applicable.

6.3   **Shelf life**
3 years

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

6.5   **Nature and contents of container**
Transparent PVC/PVDC-aluminium blisters lidded with aluminium foil

Pack sizes: 21, 30, 42, 56, 60, 90 or 100 tablets.
Calendar packs: 21, 42 tablets.

Not all pack sizes may be marketed.

6.6   **Special precautions for disposal**
No special requirements.

7   **MARKETING AUTHORISATION HOLDER**
Teva UK Limited
Eastbourne,
BN22 9AG,
England

8   **MARKETING AUTHORISATION NUMBER(S)**
PL 00289/0503

9.   **DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**
10th June 2005

10   **DATE OF REVISION OF THE TEXT**
27/06/2007
Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Lamotrigine 25, 50, 100 and 200 mg Tablets

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. What Lamotrigine is and what it is used for
   2. Before you take Lamotrigine
   3. How to take Lamotrigine
   4. Possible side effects
   5. How to store Lamotrigine
   6. Further information

1. What Lamotrigine is and what it is used for

- Lamotrigine is used to treat various types of epilepsy, including partial epilepsy with or without secondary generalisation, primary generalised epilepsy and Lennox-Gastaut Syndrome (a severe form of epilepsy).
- Lamotrigine may be used on its own to treat adults and adolescents aged 12 years and over. Lamotrigine may also be used in combination with other anti-epileptic medicines in adults and children aged 2 years and over.

[only for IE]
- Your doctor may have prescribed lamotrigine to treat other conditions if deemed necessary.

2. Before you take Lamotrigine

Do not take Lamotrigine:

- If you are allergic (hypersensitive) to lamotrigine or to any of the other ingredients of Lamotrigine Tablets.

Take special care with Lamotrigine:

- If you have previously had an allergic reaction to other anti-epileptic medicines such as phenytoin or carbamazepine
- If you develop a skin reaction – see the section ‘4. Possible side effects’
- If you have Parkinson’s disease
- If you have kidney or liver problems (your doctor may need to prescribe a lower dose)
- If you are pregnant, trying to become pregnant or breast-feeding (see also Pregnancy and breast-feeding, below)
• If you are taking oral contraceptive pills (‘the pill’) – see the section ‘Taking Lamotrigine Dispersible Tablets and contraceptives’ for more information.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Be careful if you are taking any of the following as they may interact with your medicine and your doctor may need to adjust your dose of lamotrigine:
• Anti-epileptic medicines such as valproate, carbamazepine, phenytoin, phenobarbital and primidone. The dosage of lamotrigine may need to be altered and the risk of side effects may be increased
• Hormone replacement therapy (HRT)
• The antibacterial medicine, rifampicin, as it may reduce the effect of lamotrigine
• The antidepressant medicine, sertraline, as it may increase the adverse effects of lamotrigine.

Taking Lamotrigine and Contraceptives

If you are already taking, or plan to start taking a hormonal contraceptive (‘the pill’), it is important that you discuss this with your doctor as:
• Lamotrigine may reduce the effectiveness of ‘the pill’. You should tell your doctor as soon as possible if you notice any changes in menstrual pattern, such as breakthrough bleeding or spotting. You may wish to consider other forms of contraception
• The oral contraceptive can alter the amount of lamotrigine in the blood. The amount of lamotrigine in the blood is increased during the pill-free week, which increases the risk of side effects. After the pill-free week the amount of lamotrigine in the blood is again decreased, therefore it is preferable to choose a continuous oral contraceptive (one without a ‘pill-free week’)
• Your doctor may need to change your dose of lamotrigine if you wish to start or stop taking ‘the pill’.

Pregnancy and breast-feeding

If you plan to become pregnant or find out that you are pregnant while taking these tablets, you should contact your doctor as soon as possible. It may be possible for you to continue to take lamotrigine during pregnancy so that your epilepsy is kept under control, but your doctor will need to review your treatments and monitor your lamotrigine levels before, during and after pregnancy.

Your doctor may suggest that you start taking folic acid tablets when planning to become pregnant and in the early stages of pregnancy.

You must not breast-feed while taking lamotrigine without having first discussed this with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Side effects such as dizziness and double vision can affect your ability to drive or operate machines. Therefore, before driving or using machines, you should talk to your doctor who will discuss this with you.
Important information about some of the ingredients of Lamotrigine:
- Lamotrigine tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before you take this medicinal product.
- The 100 mg tablet contains Yellow orange S (E110), which may cause allergic reactions.

3. How to take Lamotrigine

Always take Lamotrigine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The dose prescribed by your doctor depends on whether you are taking any other anti-epileptic medicines and if so, which ones. This is particularly important if you are taking medicines containing valproate.

The usual dose is:

*Adolescents and children over 12 years old:*
The usual maintenance dose used to control epilepsy is between 100 mg and 400 mg taken once a day or in two divided doses. At the start of treatment your doctor will prescribe a low dose which will be gradually increased over several weeks.

*Children between 2 and 12 years of age:*
Lamotrigine is only taken in addition to other drugs used to control epilepsy. The usual maintenance dose of Lamotrigine is between 1 mg and 15 mg per kilogram of the child’s bodyweight, taken once a day or in two divided doses. At the start of treatment your doctor will prescribe a low dose which will be gradually increased over several weeks.

*Children under 2 years of age*
Lamotrigine is not recommended for children under 2 years of age.

*Patients with liver or kidney problems*
Your doctor may reduce the usual dosage to suit your requirements.

**Method of administration**
For oral use.
The tablets should be swallowed whole with water. The tablets can be taken on an empty stomach or with a meal. Take the tablets at the same time every day, before or after meals.

*If you take more Lamotrigine than you should*
If you take more Lamotrigine than you should or if you think a child has accidentally swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Overdose can cause involuntary movement of the eyes, loss of co-ordination and drowsiness that may result in coma.

*If you forget to take Lamotrigine*
If you forget to take a tablet, take one as soon as you remember, and then go on as before. Do not take a double dose to make up for forgotten individual doses.
If you stop taking Lamotrigine
Do not suddenly stop taking Lamotrigine as this may cause seizures. Always talk to your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

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

If you suffer from any of the following symptoms **tell your doctor immediately.** If you ignore these symptoms they can lead to more serious problems. Some of these reactions are known to be more common in children, so parents should be especially aware of this:

- Unexpected skin reaction, e.g. rash and/or sore or blistering skin, mouth, eyes and/or genitals
  Skin reactions usually develop within the first 8 weeks of treatment. The chance of a skin reaction is greater if you do not follow the doctor’s dosage instructions carefully. In children, the start of a rash may be mistaken for an infection.
- Symptoms of angioedema such as: swollen face, tongue or pharynx, difficulty to swallow, hives and difficulties to breath
- If you get a high temperature, “flu like” symptoms, swollen glands or drowsiness or if your epilepsy gets worse particularly in the first month of treatment
- If you start feeling very tired, suffer from unexpected bruising or bleeding, if you suffer from more infections (e.g. colds) than usual, or if you develop a sore throat
- There have been reports of abnormalities in liver function. Symptoms of this can include yellowing of the skin, itching and abdominal (tummy) pain or tenderness. These may or may not be accompanied by a rash and feeling sick or generally unwell.

If you are unsure about any of the above, talk to your doctor, who will be able to explain more about what to look for and what to do.

The following side effects have been also reported at the approximate frequencies shown:

*Very Common (affecting more than one person in 10):*
  - Headache, dizziness
  - Double or blurred vision
  - Skin rash.

*Common (affecting fewer than one person in 10 but more than one person in 100):*
  - Irritability
  - Tiredness, drowsiness, insomnia
  - Shaking, problems with muscle co-ordination, involuntary movement of the eyes
  - Stomach disturbances, nausea, vomiting, diarrhoea.

*Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):*
  - Aggression.

*Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):*
  - Conjunctivitis (redness of the eye)
• Severe allergic reaction of the skin with (high) fever, red spots on the skin, severe skin reactions (e.g. blistering), bleeding of the lips, mouth, nose and genital areas, joint pain and/or inflammation of the eyes (Stevens-Johnson syndrome).

Very rare (affecting fewer than one person in 10,000):
• Blood disorders, including anaemia, neutropenia, leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis (these are reductions in the number of different types of blood cells), which may cause unusual tiredness or weakness, fever or chills, ulcers in your mouth or throat, unusual bleeding or unexplained bruising
• Allergic reaction of the skin with fever and blistering or peeling skin (toxic epidermal necrolysis)
• Tics – involuntary, compulsive, repetitive movements of the body
• Hallucinations, confusion, agitation
• Unsteadiness, movement disorders and uncontrolled movements
• A worsening of the symptoms in patients with pre-existing Parkinson’s disease
• Increase in seizure frequency
• Changes in liver function test results, liver problems or failure
• Lupus-like reactions, which can include a rash across the nose and cheeks, swelling and pain of the joints, muscle pain and weakness, fatigue and sun-sensitivity.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Lamotrigine

Keep out of the reach and sight of children. Do not use Lamotrigine after the expiry date which is stated on the blisters and the outer packaging. This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Lamotrigine contains:
• The active ingredient is lamotrigine 25, 50, 100 or 200 mg
• The other ingredients are lactose monohydrate, cellulose microcrystalline, starch pregelatinised, povidone K-30, silica colloidal anhydrous, sodium starch glycolate (Type A) and magnesium stearate. In addition, the 100 mg tablets contain Yellow orange S (E110) and the 200 mg tablets contain indigo carmine (E132).

What Lamotrigine looks like and contents of the pack:
• Lamotrigine 25 mg Tablets are white to off white, diamond-shaped tablets, debossed with the number “93” on one side and scored between the two numbers, debossed “39” on the other side of the tablet The tablets can be divided into equal halves.
• Lamotrigine 50 mg Tablets are white to off white, round-shaped tablets, debossed with the number “50” on one side and debossed “LT” on the other side of the tablet
• Lamotrigine 100 mg Tablets are peach, diamond-shaped tablets, debossed with the number “93” on one side and scored between the two numbers, debossed “463” on the other side of the tablet.
• 200 mg: Lamotrigine 200 mg Tablets are blue, diamond-shaped tablets, debossed with the number “93” on one side and scored between the two numbers, debossed “7248” on the other side of the tablet. The tablets can be divided into equal halves.
• Lamotrigine tablets are available in pack sizes of 21, 30, 42, 56, 60, 90 or 100 tablets. Calendar packs: 21, 42 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
{To be completed nationally}

Manufacturer
{To be completed nationally}

This medicinal product is authorised in the Member States of the EEA under the following names:
{To be completed nationally:}
{Name of the Member State}  {Name of the medicinal product}

This leaflet was last approved in {MM/YYYY}.
Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lamotrigine 25 mg tablets
Lamotrigine 50 mg tablets
Lamotrigine 100 mg tablets
Lamotrigine 200 mg tablets
Lamotrigine

2. STATEMENT OFACTIVE SUBSTANCE(S)

25 mg: Each tablet contains 25 mg lamotrigine.
50 mg: Each tablet contains 50 mg lamotrigine.
100 mg: Each tablet contains 100 mg lamotrigine.
200 mg: Each tablet contains 200 mg lamotrigine.

3. LIST OF EXCIPIENTS

25 mg: Contains lactose. See leaflet for further information
50 mg: Contains lactose. See leaflet for further information
100 mg: Contains lactose and Yellow Orange S. See leaflet for further information
200 mg: Contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
21 tablets
30 tablets
42 tablets
56 tablets
60 tablets
90 tablets
100 tablets

Calendar packs:
21 tablets
42 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Use before:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Limited
Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/0500
PL 00289/0501
PL 00289/0502
PL 00289/0503

13. BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lamotrigine 25 mg tablets
Lamotrigine 50 mg tablets
Lamotrigine 100 mg tablets
Lamotrigine 200 mg tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lamotrigine 25 mg tablets
Lamotrigine 50 mg tablets
Lamotrigine 100 mg tablets
Lamotrigine 200 mg tablets
Lamotrigine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

For calendar packs, the foil will also be printed with the days of the week
Module 5

Scientific discussion during initial procedure

1 INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted marketing authorisations for Lamotrigine 25, 50, 100 and 200mg Tablets, from Teva UK Limited for the treatment of epilepsy, generalised tonic-clonic seizure, simple partial seizures, Lennox-Gastaut syndrome and complex partial seizures.

These are applications made under Article 10.1 of 2001/83 EC for Lamotrigine 25, 50, 100 and 200mg Tablets, claiming essential similarity [Bioequivalence] to Lamictal Tablets (GlaxoSmithKline, UK), which were granted UK licences over 10 years ago.

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

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The RMS has been assured that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The products were granted marketed authorisations in the RMS (the UK) on 10th June 2005. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Teva UK Limited) gained approval for marketing authorisations in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Slovakia and Sweden.

Lamotrigine 25, 50, 100 and 200mg Tablets are available on prescription.

During the procedure, potential serious risks to public health concerns were raised by six CMS’s and the applications were referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)). These concerns were:
1. In Section 4.1 of the SPC, the indication of add-on therapy in generalised epilepsy should not be added for children from 2 years of age. The published studies referred to by the applicant are only open-label and do not adequately support the proposed indication. Furthermore this indication has not been accepted in several previous MRPs.

2. The list of indications did not include “as a mood stabiliser in bipolar disorder”, which is included for the innovator product in some member states.

3. In Section 4.6 of the SPC, one member state could not accept the wording regarding documentation from prospective pregnancy studies. These data appear to suggest that there is no increased risk of major birth defects. The wording also suggested that data on the use of lamotrigine in combination with other anti-epileptic drugs are insufficient to assess whether the risk of malformation is increased. This conclusion is rejected on statistical grounds. These data are too limited to reach this conclusion. In Section 5.3 of the SPC, the text should be amended to address the issue of potential teratogenicity of lamotrigine.

4. The waiver for omitting comparative bioavailability studies for the 50mg, 100mg and 200mg formulations has not been proven as the extrapolation of the data is based on dissolution profiles that do not demonstrate similarity.

The CMD(h) referral ended positively, with the following comments:

1. The current procedures are finalised with the Summary of Product Characteristics proposed by the UK, and only the indication for the treatment of epilepsy. The applicant has amended the text in section 4.1 of the SPC relating to children over 2 years of age:

   **Epilepsy:**

   **Adults and adolescents:**
   - Monotherapy of:
     - Partial epilepsy with or without generalisation
     - Primary generalised epilepsy

   Monotherapy in children under 12 years of age is not recommended.

   As add-on therapy in epilepsy:
   - partial seizures
   - generalised seizures
     - primary seizures
     - secondary tonic-clonic seizures
   - seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic drug combinations fail.

   **Children over 2 years of age**

   Add-on therapy in:
   - partial seizures
   - Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic agents fails.

   This medicinal product should only be started by a neurologist or paediatric neurologist with experience in the treatment of epilepsy or used in departments of neurology and similar departments.

2. Member states will address any national concerns for approving a generic marketing authorisation with fewer indications than their reference product, i.e. in this case without bipolar disorder, by including a statement in their national licence in-line with that proposed where a usage patent prevents an indication from being stated.
The applicant will include the following statement in the Patient Leaflet in Ireland for both procedures. This statement will not apply to the Patient Leaflet in other Member States. “Your doctor may have prescribed lamotrigine to treat other conditions if deemed necessary”

3. The applicant has provided a commitment that variations will be submitted to bring sections 4.6 and 5.3 of the SPC resulting from the present procedures in-line with the new text agreed for the reference products. This will also apply to any other changes that are made in relation to final approved additional pharmacovigilance statements. As an interim position, the applicant has agreed to re-introduce the following text to section 4.6 (Pregnancy) of the SPC: *Lamotrigine plasma levels should therefore be monitored before, during and after pregnancy, as well as around birth. If necessary, the dose should be adapted to maintain the lamotrigine plasma concentration on the same level as before pregnancy. In addition, dose related undesirable effects should be monitored after birth.*

4. The applicant has confirmed that the results of a further bioequivalence study performed against the French 25 mg dispersible tablets are available that support the results of the pivotal study on which the marketing authorisations were granted in the RMS. This study was completed after the updated assessment report was available. As new data could not be introduced during the procedure, the summary results of this study were only presented in the referral response document dated 06 May 2006.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Lamotrigine 25mg Tablets  
| Lamotrigine 50mg Tablets  
| Lamotrigine 100mg Tablets  
| Lamotrigine 200mg Tablets |
| Name(s) of the active substance(s) (INN) | Lamotrigine |
| Pharmacotherapeutic classification (ATC code) | N03AX09 |
| Pharmaceutical form and strength(s) | Tablets, 25mg, 50mg, 100mg and 200mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/835/01-04 |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Slovakia and Sweden |
| Name and address of manufacturer responsible for batch release in the EEA |
| 1. Teva UK Ltd., Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG. |
| 3. Teva UK Ltd, 18 Bruntcliffe Way, Morley, Leeds, W Yorkshire, LS27 0JG |
| 4. Laboratorio Belmac SA, Poligono Industrial de Malpica, Calle C. No 4, Zaragoza 50016, Spain. |
| 5. Oy Verman AB, PL152, Vanhankylantie 44b, 04400 Jarvenpaa, Finland. |
| Date of first authorisation | 10th June 2005 |
| Marketing Authorisation Number(s) | PL 00289/0500-3 |
| Name and address of the authorisation holder | TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance
The active substance is lamotrigine, which currently is not the subject of a BP or Ph Eur monograph. A detailed evaluation of the process, critical steps, process validation, process development and in-process controls have been included in the restricted sections of the Drug Master File submitted by the active ingredient manufacturer.

The active substance specification is considered adequate to control the quality of the active lamotrigine. All tests use standard Ph Eur methods. Satisfactory validation data have been provided and batch analysis data showing compliance with the specification. Active lamotrigine is stored in polyethylene bags, which are then enclosed in aluminium laminate bags for storage and distribution.

Satisfactory stability data have been provided for batches of active stored in the proposed packaging at 25°C/60%RH for 36 months and 40°C/75% RH for 6 months. The data support a retest period of 2 years.

In conclusion, active lamotrigine from this active substance manufacturer is acceptable for use in UK licensed products.

P Medicinal Product

P.1 Composition
Composition
Lamotrigine Tablet compositions contain the active substance lamotrigine (in-house) with standard pharmaceutical excipients lactose monohydrate (Ph Eur), microcrystalline cellulose (Ph Eur), pre-gelatinised starch (Ph Eur), povidone K-30 (Ph Eur), colloidal anhydrous silica (Ph Eur), sodium starch glycolate (Ph Eur), magnesium stearate (Ph Eur), yellow orange S (E110 – USP, 100mg strength only) and indigo carmine (E132 – Ph Fr, 200mg only).

Container/closure system
Finished product is packed in blisters of transparent PVC/PVdC/aluminium foil. Pack sizes are 21, 30, 42, 56, 60, 90 and 100 tablets.

P.2 Pharmaceutical development
The objective of development rationale was to produce a product with characteristics similar to the originator product, Lamictal Tablets (GlaxoSmithKline, UK).

Functions of ingredients are defined.

Comparable dissolution and impurity profiles have been provided for all strengths of Teva Lamotrigine Tablets versus Lamictal Tablets.

P.3 Method of preparation of the product
The method of manufacture is satisfactory. A satisfactory flow chart of the manufacturing process has been provided.

In-process controls during the manufacture include tablet weight, thickness, hardness and friability of uncoated tablets.
Satisfactory licences/documentation have been provided for all sites involved in the manufacture, packing, storage, batch release and quality control of the finished product.

**Process validation**

Process validation and batch data have been provided for all four strengths generated on batches representative of the production-scale. Confirmation is provided that process validation will be carried on the first three production-scale batches of the four strengths of tablets, post licensing. A prospective process validation protocol that would be used with the three production batches post licensing is provided.

**P.4 Control of other substance(s) (excipients)**

All excipients comply with their respective Ph Eur monograph. Certificates of Analysis demonstrating compliance with current Ph Eur monographs have been provided. The finished product manufacturer performs satisfactory tests as appropriate on receipt of the excipients.

Statements have been provided which confirm that no material of animal origin is used in the manufacture of the tablets.

**P.5 Control tests on the finished product**

**Finished Product Specification**

The following are tested for as part of the finished product specification:

<table>
<thead>
<tr>
<th>Tests</th>
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<tbody>
<tr>
<td>Description</td>
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<tr>
<td>Uniformity of mass</td>
</tr>
<tr>
<td>Identification</td>
</tr>
<tr>
<td>Thickness</td>
</tr>
<tr>
<td>Hardness</td>
</tr>
<tr>
<td>Friability</td>
</tr>
<tr>
<td>Assay (HPLC)</td>
</tr>
<tr>
<td>Impurities and Degradation products</td>
</tr>
<tr>
<td>Dissolution</td>
</tr>
<tr>
<td>Microbial limit test</td>
</tr>
<tr>
<td>Identification of colouring agent</td>
</tr>
</tbody>
</table>

The four strengths of tablets are differentiated by tablet size and markings. Suitable analytical test methods are provided including those for identification, assay, impurities and degradation products, dissolution, microbial controls and colouring agent identification.

HPLC methods for assay and impurities and degradation have been validated for linearity, precision (repeatability and reproducibility), accuracy, stability indicating nature by forced degradation studies, solution stability and robustness. The dissolution method has been validated for analytical parameters. Microbial method has been validated using positive controls.

Most of the analytical validation was performed using only the 25mg and 200mg strength products. This could be considered acceptable as the four strengths of the product are direct scale up or scale down versions of each other.

All reference standards used are specified and appropriate certificates of analysis provided.
Batch Analysis
Batch analyses for six pilot-scale batches have been provided, covering all strengths proposed for marketing. All results from these batches were within specifications.

P.6 Packaging Materials
The sources and specification of blister-forming materials are specified supported by certificates of analysis. All materials are food contact grade (in accordance with 90/128/EC). Appropriate tests that are carried out by the manufacturer of the drug product on receipt of each batch of packaging material.

P.7 Stability tests on the finished product
Stability data has been generated for six pilot-scale batches of finished product stored in the clear PVC packaging type proposed for marketing. Full batch histories are given for all batches on stability.

Testing was performed at 25°C/60%RH and 40°C/75% RH. Batches were also stored at 30°C/60%RH but testing was only to be performed if the accelerated product failed. The release parameters of appearance, assay, impurities and degradation products, dissolution and microbial controls were monitored during stability, using the methods as for release.

Results are available up to 24 months at real time and 6 months at accelerated storage for the 25mg and 200mg tablets with results available for 3 months for both real time and accelerated storage for the 50mg and 100mg tablet strengths.

All results were within specifications at all timepoints tested.

No in-use stability data are provided. This could be considered acceptable for a stable tablet product containing a stable active.

The applicant has committed to putting the first three production-scale batches of finished product on stability studies in accordance with CPMP/ICH guidelines

A shelf life of 24 months has been proposed for the finished product, with no specific storage conditions. This is acceptable.

Module 1 – Administrative information
MAA forms
The MAA forms are pharmaceutically satisfactory.

Summary of Product Characteristics (SPC)
The SPCs are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
The PIL is pharmaceutically satisfactory.

Packaging
The packaging is pharmaceutically satisfactory.

Module 2 – Quality overall summary
A quality overall summary, written by an appropriately qualified person, has been provided and is satisfactory, non-critical summary of Module 3.
Conclusions on quality
The pharmaceutical assessor concluded that marketing authorisations may be granted for these products.

III.2 PRE-CLINICAL ASPECTS
These applications for a generic product claim essential similarity to Lamictal 25mg, 50mg, 100mg and 200mg Tablets licensed to GlaxoSmithKline, which have been licensed within the UK for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology
The applicant has sponsored a single-dose, randomised, blinded comparative bioavailability study comparing 2 x 25 mg test product against corresponding dose of two tablets of reference product. The study was performed as a four-way crossover with 2-week washouts in 24 healthy volunteers given the following products.

Test (A) : Lamotrigine 25mg tablets
Test (B) : Lamotrigine 25mg dispersible tablets
Reference (C) : Lamictal 25mg tablets from Wellcome/GSK (UK product).
Reference (D) : Lamictal 25mg dispersible tablets from Wellcome/GSK (UK product).

Certificates of analysis have been provided for all batches used in the bioequivalence study and are satisfactory. Samples were analysed by reverse-phase HPLC, with a UV detector and pindolol as an internal standard. The method is adequately validated. Pharmacokinetic parameters of AUC, C_{max} and T_{max} were determined and analysed by ANOVA for statistical treatment for ratio test/reference and 90% confidence intervals.
The results are presented below:

<table>
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<tr>
<th></th>
<th>Mean $\text{AUC}_{\text{inf}}$ (ng.hr/ml)</th>
<th>mean $\text{C}_{\text{max}}$ (ng/ml)</th>
<th>Median $\text{T}_{\text{max}}$ (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (TEST, tablet)</td>
<td>31358.95</td>
<td>679.75</td>
<td>1.00 [0.33-4.00]</td>
</tr>
<tr>
<td>C (REFERENCE, tablet)</td>
<td>31070.06</td>
<td>663.12</td>
<td>1.00 [0.33-3.00]</td>
</tr>
<tr>
<td>A / C</td>
<td>1.01</td>
<td>1.03</td>
<td>/</td>
</tr>
<tr>
<td>90% CONFIDENCE INTERVALS</td>
<td>0.93-1.09</td>
<td>0.97-1.08</td>
<td>/</td>
</tr>
</tbody>
</table>

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<tr>
<th></th>
<th>ANOVA</th>
<th>MANN-WHITNEY</th>
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<td>N.S.</td>
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<table>
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<tr>
<th></th>
<th>Mean $\text{AUC}_{\text{inf}}$ (ng.hr/ml)</th>
<th>mean $\text{C}_{\text{max}}$ (ng/ml)</th>
<th>Median $\text{T}_{\text{max}}$ (hrs)</th>
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</thead>
<tbody>
<tr>
<td>B (TEST, dispersible)</td>
<td>30163.87</td>
<td>646.98</td>
<td>1.25 [0.33-3.50]</td>
</tr>
<tr>
<td>D (REFERENCE, dispersible)</td>
<td>32490.40</td>
<td>666.30</td>
<td>1.00 [0.33-2.50]</td>
</tr>
<tr>
<td>B / D</td>
<td>0.93</td>
<td>0.97</td>
<td>/</td>
</tr>
<tr>
<td>90% CONFIDENCE INTERVALS</td>
<td>0.86-1.00</td>
<td>0.92-1.03</td>
<td>/</td>
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<table>
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<th></th>
<th>ANOVA</th>
<th>MANN-WHITNEY</th>
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<td>N.S.</td>
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These values are within the accepted regulatory range of 80-125% (0.80-1.25 range), indicating that A is bioequivalent to C and B is bioequivalent to D in this bioequivalent study. Dose proportionality and linearity across the therapeutic range have been stated by the applicant as has the power of the study. Thus bioequivalence has been demonstrated for the 25mg, 50mg, 100mg and 200mg strengths.

### III.3.2 Clinical Efficacy
No new data.

### III.3.3 Clinical Safety
No new data

**Module 1 – Administrative information**

*MAA forms*

The MAA forms are medically satisfactory.

*Summary of Product Characteristics (SPC)*

The SPCs are medically satisfactory.

*Patient Information Leaflet (PIL)*

The PIL is medically satisfactory.
Packaging
The packaging is medically satisfactory.

Module 2 – Clinical overall summary
A clinical overall summary, written by an appropriately qualified person, has been provided and is satisfactory, non-critical summary of Module 5.

Conclusions on safety
The medical assessor concluded that marketing authorisations may be granted for these products.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The important quality characteristics of Lamotrigine 25mg, 50mg, 100mg and 200mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Lamotrigine 25mg tablets and Lamictal 25mg Tablets. As the four strengths of the proposed product tablets are dose proportional, with direct scale-up and scale-down versions of each other, and exhibit similar dissolution profiles, the results and conclusions of the bioequivalence study on 25mg strength could be extrapolated to the three higher strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product in the RMS.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with lamotrigine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

During the procedure, potential serious risk to public health concerns were raised by several CMS’s and a CMD(h) referral was initiated. These issues were satisfactorily resolved and a recommendation to grant the licences in all concerned member states was made. A summary of the reasons for and comments from the CMD(h) referral is given in the introduction to Module 5 of this document.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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