SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lamotrigine 25 mg tablets
Each tablet contains 25 mg lamotrigine.
Excipient: 48.75 mg lactose monohydrate/tablet

Lamotrigine 50 mg tablets
Each tablet contains 50 mg lamotrigine.
Excipient: 97.50 mg lactose monohydrate/tablet

Lamotrigine 100 mg tablets
Each tablet contains 100 mg lamotrigine.
Excipient: 195.00 mg lactose monohydrate/tablet

Lamotrigine 200 mg tablets
Each tablet contains 200 mg lamotrigine.
Excipient: 390.00 mg lactose monohydrate/tablet

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet. Light yellow coloured, round, flat tablets with a breakline on one side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents
- partial epilepsy with or without generalisation
- primary generalised epilepsy

Children aged 2 to 12 years:
- Add-on therapy for refractory partial epilepsy.
Adults, adolescents and children over 2 years of age:
- Add-on therapy for Lennox-Gastaut-Syndrome when other available anti-epileptic drug combinations fail.

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

4.2 Posology and method of administration

To achieve the maintenance dose, the weight of a paediatric patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine is not equal to whole or halved tablets, the dose to be administered should be that of lower number strength of whole or halved 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When concomitant antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or other antiepileptic drugs are added-on to treatment regimes containing lamotrigine consideration should be given to the effect this may have on the pharmacokinetics of different active substances, including lamotrigine (see section 4.5).

In patients taking antiepileptic drugs 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).

Adults and adolescents

Monotherapy (see Table 1)

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

Add-on therapy with other antiepileptic drugs (see Table 1)

Patients, who receive valproate with or without other antiepileptics (see section 4.5)

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

Patients, who receive other antiepileptics or other active substances that induce the metabolism of lamotrigine with or without antiepileptics except valproate (see section 4.5)

The initial dose is 50 mg/day once daily for 2 weeks, then 100 mg/day given in 2 divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1 to 2 weeks until optimum response is achieved. The usual maintenance dose is 200-400 mg/day given in 2 divided doses. Some patients have required 500-700 mg/day to achieve the desired response.

Patients, who receive oxcarbazepine without other active substances that interfere lamotrigine metabolism (see section 4.5)

The initial dose is 25 mg once daily for two weeks, then 50 mg once daily for two weeks. Thereafter, the dose should be increased by a maximum of 50-100 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose is 100-200 mg/day given once daily or in 2 divided doses.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Week 1 + 2</th>
<th>Week 3 + 4</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>25 mg (once daily)</td>
<td>50 mg (once daily)</td>
<td>100-200 mg (once daily or in 2 divided doses)</td>
</tr>
<tr>
<td>Add-on treatment with valproate with or without other antiepileptic drugs</td>
<td>12.5 mg (25 mg every other day)</td>
<td>25 mg (once daily)</td>
<td>100-200 mg (once daily or in 2 divided doses)</td>
</tr>
<tr>
<td>Add-on treatment with enzyme-inducing antiepileptic drugs* with or without other antiepileptic drugs (no valproate)</td>
<td>50 mg (once daily)</td>
<td>100 mg (in 2 divided doses)</td>
<td>200-400 mg (in 2 divided doses)</td>
</tr>
<tr>
<td>Add-on treatment with oxcarbazepine without other enzyme-inducers or -inhibitors</td>
<td>25 mg (once daily)</td>
<td>50 mg (once daily)</td>
<td>100-200 mg (once daily or in 2 divided doses)</td>
</tr>
</tbody>
</table>

* e.g. phenytoin, carbamazepine, phenobarbital, primidone or other enzyme-inducers (see section 4.5)
Children aged 2 to 12 years

Add-on therapy with other antiepileptic drugs (see Table 2)

*Children, who receive valproate with/without other antiepileptic drugs*

The initial dose of lamotrigine is 0.15 mg/kg/day once daily for 2 weeks, followed by 0.3 mg/kg/day once daily for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1 to 2 weeks until optimal response is achieved. The usual maintenance dose is 1-5 mg/kg/day given once daily or in 2 divided doses.

*Children, who receive enzyme-inducing antiepileptic drugs or other enzyme-inducing active substances with/without other antiepileptic drugs except valproate*

The initial dose of lamotrigine is 0.6 mg/kg/day given in 2 divided doses for 2 weeks, followed by 1.2 mg/kg/day given in 2 divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1 to 2 weeks until optimal response is achieved. The usual maintenance dose is 5-15 mg/kg/day given in 2 divided doses.

*Children, who receive oxcarbazepine without enzyme-inducing or-inhibiting active substances*

The initial dose of lamotrigine is 0.3 mg/kg/day given once daily or in 2 divided doses for 2 weeks, followed by 0.6 mg/kg/day given once daily or in 2 divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every 1 to 2 weeks until optimal response is achieved. The usual maintenance dose is 1-10 mg/kg/day given in 2 divided doses, with a maximum dose of 200 mg/day.

*Table 2*

Recommended dose escalation of lamotrigine for combination therapy in children from 2 to 12 years (total daily dose in mg/kg body weight/day)

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Week 1 + 2</th>
<th>Week 3 + 4</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on treatment with valproate with or without other antiepileptic drugs</td>
<td>0.15 mg/kg(^*) (once daily)</td>
<td>0.3 mg/kg (once daily)</td>
<td>1-5 mg/kg (once daily or in 2 divided doses) to achieve maintenance, the daily dose should be increased by a maximum of 0.3 mg/kg every 1 to 2 weeks, up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

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SPC-Day 90
**Add-on treatment with enzyme-inducing antiepileptic drugs**

|                      | 0.6 mg/kg (in 2 divided doses) | 1.2 mg/kg (in 2 divided doses) | 5-15 mg/kg (in 2 divided doses) |
|----------------------|-------------------------------|-------------------------------|---------------------------------
| Add-on treatment     |                               |                               |                                  |
| with enzyme-inducing  |                               |                               |                                  |
| antiepileptic drugs  |                               |                               |                                  |
| * (no valproate)     |                               |                               |                                  |
|                      |                               |                               | to achieve maintenance, the daily dose should be increased by a maximum of 1.2 mg/kg every 1 to 2 weeks, up to a maximum dose of 400 mg/day |

**Add-on treatment with oxcarbazepine without other enzyme-inducers or inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg/kg (once daily or in 2 divided doses)</th>
<th>0.6 mg/kg (once daily or in 2 divided doses)</th>
<th>1-10 mg/kg (once daily or in 2 divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with oxcarbazepine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>enzyme-inducers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to achieve maintenance, the daily dose should be increased by a maximum of 0.6 mg/kg every 1 to 2 weeks, up to a maximum dose of 200 mg/day</td>
</tr>
</tbody>
</table>

* e.g. phenytoin, carbamazepine, phenobarbital, primidone or other enzyme-inducers (see section 4.5)

**NOTE:** Depending on the body weight of the child the recommended dose cannot be achieved for all children with the current strengths of this medicinal product. Other lamotrigine products with less active substance are available for those children. If the calculated dose is less than 1 mg lamotrigine, lamotrigine should not be used.

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

**Special patient groups**

**Children below 2 years of age**
There is insufficient information available about the use of lamotrigine in children under 2 years.

**Elderly patients (>65 years of age):**
No dose 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 be generally reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and by 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.
Depending on the dose, the recommended dose may not be performable in patients with hepatic impairment with the current strengths of this medicinal product (see section 5.2).

**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).
Combined with oral hormonal contraceptives
It is recommended that patients already using lamotrigine and wanting to start oral hormonal contraception, use a continuous contraceptive (see sections 4.4 and 4.5).

A distinction can be made between the following situations:

Patients on a maintenance dose of Lamotrigine tablets who are starting on oral contraceptives and who use no additional inducers of lamotrigine glucuronidation:

Whenever a woman starts using oral hormonal contraceptives, in most cases the maintenance dose of lamotrigine will have to be doubled (see sections 4.4 and 4.5). The plasma levels of lamotrigine should be measured before and after the start of oral hormonal contraception in order to maintain the baseline levels and, if necessary, the dose should be adjusted. Increases in the dosage should take place according to the recommended dose escalation.

Patients on a maintenance dose of Lamotrigine tablets and oral hormonal contraceptives, who are withdrawing oral hormonal contraception and who use no additional inducers of lamotrigine glucuronidation:

In most cases the maintenance dose of lamotrigine will have to be reduced by 50% according to the individual clinical response (see sections 4.4 and 4.5). The dosage should also be adjusted according to the individual plasma levels and/or the clinical response (the incidence of dose-related undesirable effects). The plasma levels of lamotrigine should be measured before and after withdrawing oral contraception in order to maintain the baseline levels and if necessary the dose should be adjusted.

It is recommended that, after withdrawing oral hormonal contraception, the daily dose of lamotrigine be gradually reduced by 50-100 mg a week over a period of 3 weeks.

Starting Lamotrigine combined with continuous use of hormonal contraceptives:

The normal dosages can be applied.

Restarting therapy

The need for escalation to maintenance dose should be carefully assessed when restarting lamotrigine in patients who have discontinued it for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see section 4.4). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see section 5.2), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule.

Method of administration
Lamotrigine tablets should be swallowed with a little water.

4.3 Contraindications

Hypersensitivity to lamotrigine or to any of the excipients

4.4 Special warnings and precautions for use

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 skin rashes are mild and self-limiting. Rarely serious skin rashes including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).

Reports from epilepsy studies in adults with current dosing recommendations have shown an approximate serious skin rashes incidence of 1 in 500, but studies suggest that the incidence of rashes associated with hospitalisation in children under the age of 12 is higher (1/300 to 1/100). The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000.

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of an active substance reaction in children that develop symptoms of rash and fever during the first 8 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 sections 4.2 and 4.5).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine should be withdrawn immediately and not be restarted unless the rash is clearly not active substance 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 the 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 or symptoms develop. If such signs or 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 (e.g. 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 drugs, see sections 4.2 and 4.5). Lamotrigine can increase attacks in some patients.

Folic acid metabolism

Lamotrigine is a weak inhibitor of dihydrofolate acid reductase hence there is a possibility of interference with folic acid metabolism during long-term therapy (see section 4.5).

Other organs

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

Use in combination with oral hormonal contraceptives

The effect of contraception on the efficacy of lamotrigine

A combination of 30 micrograms of ethinylestradiol and 150 micrograms of levonorgestrel has been shown to cause a twofold increase in the clearance of lamotrigine (see section 4.5). A reduction in lamotrigine levels has been associated with loss of seizure control. Following the dose escalation of lamotrigine, a higher dose of lamotrigine may be necessary (up to double) in order to achieve an maximal therapeutic response. When oral hormonal contraceptives are withdrawn, the clearance of lamotrigine can halve. This is linked to dose-related undesirable effects. The patient should be monitored for these. In women using no enzyme inducers and taking oral hormonal contraceptives which involve a week of inactive medication (e.g. a 'pill-free week'), temporary gradual increases in lamotrigine levels may occur during the week of inactive medication. These increases will be greater when the dose of lamotrigine is increased in the days before or during the week of inactive medication (see section 4.5).

Oral hormonal contraceptives involving a week of inactive medication are not recommended for women on lamotrigine. During the pill-free or placebo week, the lamotrigine levels show up to a twofold increase and after starting a new pack of oral hormonal contraceptives the lamotrigine levels fall again.

This degree of fluctuation in plasma levels of AEDs is not recommended. Starting/stoping oral hormonal contraception without adjusting the dose of lamotrigine is linked to loss of seizure control and the occurrence of dose-related undesirable effects respectively. It has not been evaluated whether the increases in the plasma concentration of lamotrigine induced by the pill-free or placebo week also cause these undesirable effects. It is not known whether the rapid drop in the plasma level of lamotrigine during the week that the oral hormonal contraception is re-introduced induces seizures. It is recommended that patients already taking lamotrigine and wanting to start oral hormonal contraception, use a continuous contraceptive (see section 4.5).

During pregnancy, the plasma levels of lamotrigine fluctuate considerably (see section 4.6).

There are no studies on other oral hormonal contraceptives and hormone replacement therapy (HRT) but they may have a similar effect on the pharmacokinetics of lamotrigine.
The effect of lamotrigine on contraception
If lamotrigine and an oral hormonal contraceptive (a combination of 30 micrograms of ethinylestradiol and 150 micrograms of levonorgestrel) are administered simultaneously, a slight increase in the clearance of levonorgestrel and changes in serum FSH and LH might occur (see 4.5 “Interaction with Other Medicaments and Other Forms of Interaction”). The impact of these changes on ovarian activity is unknown. Reduced effectiveness in contraception cannot be excluded. Patients should therefore be instructed to report immediately any changes in their menstrual pattern (e.g. breakthrough bleeding).

Renal impairment
Caution should be exercised in treating patients with renal failure, because the half-life of lamotrigine may be extended in case of severe impaired renal function. Accumulation of the glucuronide metabolite is to be expected too.

Hepatic impairment
The main pathway of elimination is hepatic metabolism. Based on pharmacokinetic data in subjects with hepatic failure dose adjustment is recommended according to severity (Child-Pugh classification).

Lactose intolerance
This medicinal product contains lactose monohydrate. Patients with rare hereditary disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
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 antiepileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentration of concomitant antiepileptic drugs. In vitro studies indicate that lamotrigine does not displace other antiepileptic drugs from protein binding sites.

The effect of lamotrigine on the pharmacokinetics of oral hormonal contraception
Steady state doses of 300 mg of lamotrigine had no pharmacokinetically relevant effect (7% decrease) on the AUC in the steady-state of the ethinylestradiol component (30 micrograms) resulting in a average decrease of 19% in the AUC of 12% in the Cmax.. A
slight increase was observed in the overall clearance of the levonorgestrel component (150 micrograms of levonorgestrel). Measurement of serum FSH, LH and estradiol during the study indicated some loss of suppression in ovarian hormonal activity in some women. However, measuring serum progesterone showed no hormonal evidence of ovulation in any of the 16 woman included. The impact of the slight 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 active substance metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). Half-life of lamotrigine is shortened to approximately 14 hours, in children below 12 years: approximately 7 hours. Valproate reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly 2 fold (see sections 4.2 and 4.4). 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>Phenytoin</td>
<td>Primidone</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Rifampicine**</td>
<td></td>
<td>Oxcarbazepine**</td>
</tr>
<tr>
<td>Ethinyloestradiol/Levonorgestrel combination*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Other oral contraceptive and 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 Cmax and 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 Cmax. Adverse events were reported more frequently with oxcarbazepine and lamotrigine than with either monotherapy. The most common adverse events were headache, dizziness, nausea and somnolence.

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

**The effect of oral hormonal contraception on the pharmacokinetics of lamotrigine**

In a study of 16 female volunteers, 30 micrograms ethinylestradiol/150 micrograms levonorgestrel in a combined oral hormonal contraceptive pill caused around a two-fold increase in lamotrigine overall clearance, resulting in an average decrease of 52% in the AUC and 39% in Cmax, respectively. Serum lamotrigine concentrations gradually increased during the pill-free week. At the end of the pill-free week the lamotrigine concentration was approximately twice as high as during simultaneous treatment with ethinylestradiol/levonorgestrel. See also section 4.4.
Antipsychotic active substances
The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine.
Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.
In 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, it did not induce 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

Woman and childbearing potential/Contraception

Women with a wish to become pregnant and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations may be enhanced in combination therapy with other anticonvulsants.

Oral hormonal contraceptives involving a week of inactive medication are not recommended for woman ion Lamotrigine (see section 4.4).

Pregnancy

Woman with epilepsy who wish to become pregnant are advised to consult their doctor.

Withdrawing anti-convulsive therapy is not recommended. Treating epilepsy during pregnancy is a clinical dilemma. On one hand there is a risk of congenital abnormalities, on the other hand the loss of seizure control is potentially life threatening for mother and child. Serum lamotrigine concentrations could gradually decrease during the course of the pregnancy.
After birth the plasma level of lamotrigine could rise rapidly with a risk of dose-related undesirable effects. Plasma levels of lamotrigine should therefore be monitored before, during and after pregnancy and during parturition. If necessary, the dose should be adjusted to maintain the pregnancy level of lamotrigine. In addition, checks should be made after the birth for dose-related side-effects.
Experience to date (1000) in using lamotrigine as monotherapy during the first trimester did not reveal an increased risk of congenital abnormalities. It is known that newborn children from mothers who use antiepileptic drugs or suffer from epilepsy more frequently have developmental disorders/congenital abnormalities than other babies. The risk of harmful
effects on the foetus appears to be higher in combination with other anti-epileptic drugs. This has also been observed in polytherapy with lamotrigine and valproate. Reproductive toxicity has been observed in animal studies with lamotrigine (see section 5.3). Lamotrigine is a weak inhibitor of dihydrofolic acid reductase. Folic acid supplements (at standard doses for any pregnant women) are strongly recommended.

Lactation
Lamotrigine is excreted into breast milk and may reach serum concentrations which may result in pharmacological effects in the breast-fed infant. The benefit of breastfeeding should be weighed against the possible risk of the occurrence of undesirable effects in the baby.

If the infant is breast-fed, he/she should be monitored for possible effects.

4.7 Effects on ability to drive and use machines

Neurological effects like dizziness and blurred vision have been reported when treating with lamotrigine. Given the profile of the undesirable effects, it should be taken into consideration, that lamotrigine can have an major influence on the ability to drive and use machines.

Therefore the patient should wait and see how Lamotrigine affects him before he drives or operate machines.

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>Skin and Subcutaneous tissue disorders</td>
<td>Skin rash”</td>
<td>Stevens Johnson Syndrome</td>
<td>Toxic epidermal Necrolysis</td>
<td></td>
</tr>
</tbody>
</table>

SPC-lamotrigine-mibe-122005 12
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 8 weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4).

Serious skin rashes are common in children (1%) and uncommon in adults (0.3%). Skin rashes are more common, when lamotrigine is taken with other antiepileptic drugs. 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 active substance withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

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

- High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- Concomitant use of valproate (see section 4.2)

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation (DIC), multi-organ failure, see section 4.4).

2) Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, 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
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 and treatment with activated charcoal for suspected intoxication 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
Mode of action:  
The results of pharmacodynamic studies suggest that lamotrigine is a blocker of voltage-sensitive sodium channels. It blocks voltage-dependent sustained, repetitive impulses in cultured neurons and inhibits pathological release of glutamate (amino acid which plays a key role in the generation of seizures), as well as glutamate-evoked bursts of action potentials.

5.2 Pharmacokinetic properties

Absorption  
Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentration occur approximately 2-3 hours after oral administration. High interindividual variability in peak plasma concentration at steady state prevails. 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.

Distribution  
55% of lamotrigine is bound to plasma proteins. It is very unlikely that displacement from plasma protein would result in toxicity. The volume of distribution is approximately 0.9-1.2 L/kg.

Metabolism  
Lamotrigine induces its own metabolism to a modest extent depending on the dose. This leads to a 25% decrease in half-life at steady state when 150 mg is administered twice daily. However, there is no evidence that lamotrigine affects the pharmacokinetics of other antiepileptic drugs and data suggest that interactions between lamotrigine and active substances metabolised by cytochrome P450 enzymes are unlikely. UDP-glucuronyltransferases are responsible for the metabolism of lamotrigine. The main metabolite found in the urine is 2-N glucuronide which corresponds to 65% of the dose.

Elimination  
The clearance and half-life are independent of the dosage. The mean elimination half-life in healthy adults is 24 to 35 hours. Mean steady-state clearance in healthy volunteers is 39±14 mL/min. Clearance occurs predominantly by metabolism, followed by elimination of glucuronated metabolites in the urine. Less than 10% is eliminated unchanged in the urine, while approximately 2% is excreted in the faeces. In a study in subjects with Gilbert’s syndrome (glucuronyltransferase deficiency), the mean apparent clearance was reduced by 32% compared with the control group, but the values are within the normal range for the general population. The half-life of lamotrigine is considerably affected by concomitant treatment. Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing active substances such as carbamazepine or phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see section 4.2).

Special patients groups  
Children  
Clearance adjusted for body weight is higher in children than in adults with the highest values
in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing active substances such as carbamazepine and phenytoin and increasing to mean values of 45-50 hours when co-administered with valproate alone (see section 4.2).

**Elderly**

Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39 mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg.

**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 the pharmacokinetics of lamotrigine are little affected, but that the plasma concentrations of the major glucuronide metabolite increased almost 8-fold due to reduced renal clearance.

**Impaired hepatic function**

A single dose pharmacokinetic study was performed in 24 patients with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24 and 0.10 mL/min in patients with grade A, B and C (Child Pugh classification) hepatic impairment, respectively, compared to 0.34 mL/min in the healthy controls. Half-life: 36, 60, or 110 hours versus 32 hours in controls. Reduced doses should generally be used in patients with grade B and C hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Lamotrigine was not teratogenic in mice and rabbits in dosages comparable to the maximum human dosage. Structural changes were observed in rat fetuses after oral administration of lamotrigine to pregnant rats during organogenesis. Furthermore, in rat and mice, a decreased fetal body weight and decreased bone formation and in rats behavioural effects and an increase in pre- and postnatal deaths were observed after administration of lamotrigine during pregnancy. In addition decreased fetal folic acid concentrations were observed in animal studies. Other animal studies did not reveal any particulars which are relevant for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose (E460)
Povidone K 30 (E1201)
Iron oxide yellow (E172)
Sodium starch glycolate (type A)
Magnesium stearate (E470b)
Talc (E553b)
Silica colloidal anhydrous (E551)

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 the container
Lamotrigine 25 mg tablets:
10, 28, 30, 50, 56, 90, 100 tablets in Aluminium/PVC blisters).

Lamotrigine 50 mg, 100 mg, 200 mg tablets:
10, 28, 50, 56, 90, 100, 200 tablets in Aluminium/PVC blisters).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste material derived from such medicinal product and other handling of the product
No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
November 2005
December 2005